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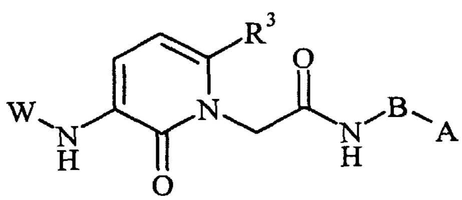
(54) Title: THROMBIN INHIBITORS



(I)

(57) Abstract: Novel thrombin inhibitors of the formula I (I)and pharmaceutically acceptable salts thereof are described wherein the substituents in the description have the specific meanings. The compounds are useful as thrombin inhibitors.

THROMBIN INHIBITORS

The invention belongs to the field of pharmaceutical industry and relates to novel heterocyclic derivatives of tripeptides and tripeptide mimetics, methods for their preparation and pharmaceutical compositions containing them.

Heterocyclic derivatives of tripeptides and tripeptide mimetics are inhibitors of thrombin and other serine proteases which play a role in blood coagulation and which have the anticoagulant activity. Nowadays, heparins and coumarins predominantly used for inhibition of coagulation *in vivo* have a number of untoward and unexpected effects. There is, therefore, a constant need for new substances with anticoagulant activity.

Serine protease thrombin is a key enzyme in the processes of blood coagulation and thus in the development of thrombosis. Its principal action is to convert soluble fibrinogen into insoluble fibrin which forms a mechanical matrix of the blood clot. In addition, it mechanically strengthens the clot by activating factor XIII which covalently links fibrin monomers and stimulates platelet aggregation. By a positive feedback mechanism via activation of factors V and VIII the thrombin concentration at the site of injury is increased. With the above role played in hemostasis, thrombin has become a target molecule for the development of new anticoagulants (Sanderson P.E.J., Naylor-Olsen A.M. *Curr. Med. Chem.* 1998, *5*, 289-304.; Menear K. *Curr. Med. Chem.* 1998, *5*, 457-468.; Breznik M., Pečar S. *Farm. vestn.* 1997, *48*, 545-560; Sanderson P. E. J. *Med. Res. Rev.* 1999, *19*, 179-197).
The active site of thrombin with the characteristic catalytic triad (Asp 189, His 57, Ser 195) can be divided into three binding areas: S1 pocket giving the enzyme specificity for the basic part of the inhibitor molecule P1, S2 hydrophobic area which prevents access of the inhibitors and the substrate to the active site, and a larger S3 hydrophobic area (Bode W., Mayr I., Baumann U. et al. *The EMBO Journal* 1988, *8,* 3467-3475).
Based on the knowledge of the crystalline structure of thrombin, a number of low molecular weight inhibitors have been developed which act at the thrombin active site. An ideal thrombin inhibitor should have good bioavailability, long half-life and be suitable for oral administration. Achievement of these aims is limited either by a basic guanidine or amidine group, present in P1 moiety of many known thrombin inhibitors or by a reactive electrophilic group, present in electrophilic thrombin inhibitors, for example - in efegatran-and PPACK. An important criterion in designing thrombin inhibitors is also the selectivity to other serine proteases, such as trypsin, factor Xa, urokinase, tissue plasminogen activator and plasmin

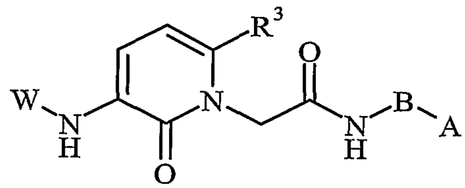
(Kimball S.D. *Current Pharmaceutical Design* 1995, *1*, 441-468.; Das J., Kimball S.D. *Bioorg. Med. Chem.* 1995, *3*, 999-1007).

Low molecular weight inhibitors of the thrombin active site mimic a tripeptide sequence D-Phe-Pro-Arg which binds to the thrombin active site. The first phase in the development were irreversible inhibitors which covalently react with Ser 195 at the active site. PPACK is a prototype of this type of inhibitor having a high reactivity. Argatroban is the first highly effective and selective reversible inhibitor available on the market. A large number of structurally different, active reversible inhibitors with hydrophilic basic groups having low bioavailability after oral administration have been synthesised to date (Menear K. *Curr. Med. Chem.* 1998, *5*, 457-468).

By extensive modification of the P1 part of thrombin inhibitors, primarily by substituting basic guanidine or amidine groups with neutral or weakly basic groups, their bioavailability can be increased. Larger groups in this part of the molecule lead to higher selectivity of the inhibitors for thrombin as, compared to the majority of other serine proteases, thrombin has relatively large S1 pocket. Selectivity of thrombin inhibitors is generally estimated regarding their ability for inhibition of trypsin which by form and size of the active site is most closely related to thrombin and has a smaller S1 pocket. Modification of other parts of the molecule (P2 and P3), especially substitution of the ester and amide bonds, may further increase the stability of thrombin inhibitors in the body. Such thrombin inhibitors are less sensitive to nonspecific proteases and hydrolysis and consequently their half-life increases (Menear K. *Curr. Med. Chem.* 1998, 5, 457-468.; Tucker T.J., Brady S.F., Lumma W.C. et al. *J. Med. Chem.* 1998, *41*, 3210-3219).

An object of the invention is, therefore, to provide novel compounds suitable for the use in therapy or in manufacturing novel medicaments.

This object is achieved for example by the combination of the features defined in each of the claims.
According to one aspect of the invention the object is achieved for example by the novel compounds of the general formula I



(I)

wherein:

W is

R^1,

R^1OCO,

R^1CO,

R^1SO_2,

$(R^1(CH_2)_n)_mNH_qCO$, where n is 0, 1, 2, 3 or 4, where m is 1 or 2 and where q is 0 or 1, with the proviso that where n is 1, 2, 3 or 4, q is 1 and m is 1, and where n is 0, m is 1 or 2 and q is 0 or 1, and where n is 0, m is 2 and q is 0, and wherein R^1 can be the same or different;

R^1 is

$R^2(CH_2)_n$, where n is 0, 1, 2, 3 or 4,

$(R^2)(OR^2)CH(CH_2)_p$, where p is 1, 2, 3 or 4,

$(R^2)_2CH(CH_2)_n$, where n is 0, 1, 2, 3 or 4, and R^2 can be the same or different, and

$R^2O(CH_2)_p$, where p is 1, 2, 3 or 4;

R^2 is

hydrogen,

phenyl, unsubstituted or substituted with one or more C_{1-4} linear or branched alkyl, C_{1-4} linear or branched alkoxy, halogen, trifluoromethyl, hydroxy, $COOR^4$, $CONHR^4$, nitro, NHR^4 or NR^4R^4 group(s),

naphthyl,

biphenyl,

5- to 7-membered monocyclic or 9- to 10- membered bicyclic heterocyclic ring system which can be substituted or unsubstituted and which, in addition to carbon atoms, contains up to 3 heteroatoms selected from N, O and S,

$COOR^4$,

C_{1-4} linear or branched alkyl,

C_{3-7} cycloalkyl, or

C_{7-12} bicycloalkyl;

R^4 is

hydrogen, or

C_{1-4} linear or branched alkyl;

R^3 is

hydrogen,

C_{1-4} linear or branched alkyl,

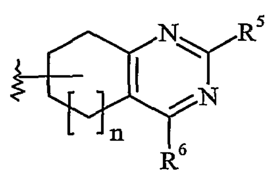
C_{3-7} cycloalkyl, or

trifluoromethyl group;

B is

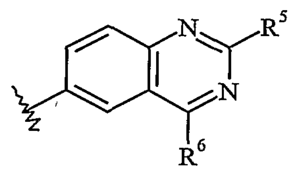
$(CH_2)_k$, where k is 0 or 1; and

A is chosen from one of the following radicals:

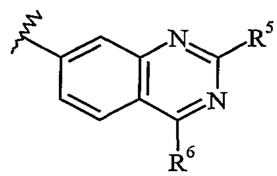
- 

n = 0 or 1

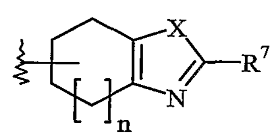
(substituted 6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine, attached to group B via the position 5, 6 or 7 or substituted 5,6,7,8-tetrahydroquinazoline, attached to group B via the position 5,6,7 or 8);

- 

(substituted quinazoline, attached to group B via the position 6);

- 

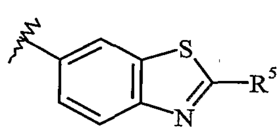
(substituted quinazoline attached to group B via the position 7);

- 

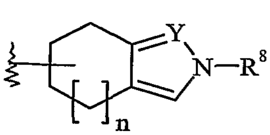
n = 0, 1

wherein X is S, NH or O

(substituted 1,4,5,6-tetrahydrocyclopenta[*d*]-imidazole, 5,6-dihydro-4*H*-cyclopenta[*d*][1,3]-thiazole, 5,6-dihydro-4*H*-cyclopenta[*d*][1,3]-oxazole, attached to group B via the position 4, 5 or 6 or substituted 4,5,6,7-tetrahydro-1,3-benzothiazole, 4,5,6,7-tetrahydro-1*H*-benzimidazole or 4,5,6,7-tetrahydro-1,3-benzoxazole, attached to group B via the position 4, 5, 6 or 7);

- 

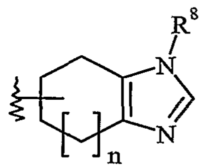
(substituted 1,3-benzothiazole, attached to group B via the position 6);

- 

n = 0, 1

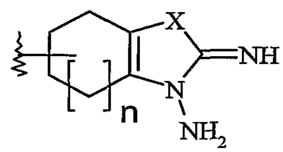
wherein Y is N or CH

(substituted 2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole, 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole, attached to group B via the position 4, 5 or 6 or substituted 4,5,6,7-tetrahydro-2*H*-indazole, 4,5,6,7-tetrahydro-2*H*-isoindole, attached to group B via the position 4, 5, 6 or 7);

- 

  n = 0, 1

  (substituted 5,6-dihydro-4*H*-cyclopenta[*d*]imidazole, attached to group B via the position 4, 5 or 6
  or
  substituted 4,5,6,7-tetrahydro-1*H*-benzimidazole, attached to group B via the position 4, 5, 6 or 7);

- 

  n = 0, 1

  wherein X is O or S

  (substituted 2-imino-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]-thiazol-3-ylamine, 2-imino-5,6-dihydro-4*H*-cyclopenta[*d*][1,3]-oxazol-3-ylamine
  attached to group B via the position 4, 5 or 6
  or
  (substituted 2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-3(2*H*)-ylamine, substituted 2-imino-4,5,6,7-tetrahydro-1,3-benzoxazol-3(2*H*)-ylamine attached to group B via the position 4,5,6 or 7).

R^5 is

hydrogen or NH_2;

R^6 is

hydrogen or NH_2;

R^7 is

hydrogen, NH_2 or $NHC(NH)NH_2$, and

R^8 is

hydrogen, CH_3, ethyl, propyl, cyclopropyl or $C(NH)NH_2$.

A further aspect of the invention is the use of the compounds of formula I according to the invention in therapy or for manufacturing novel medicaments for inhibiting thrombin and fibrin formation and for inhibiting thrombus formation in man and other mammals.

A further aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of the compounds of the invention and the use of this pharmaceutical composition for inhibiting thrombin or inhibiting formation of fibrin in blood of man or mammals.

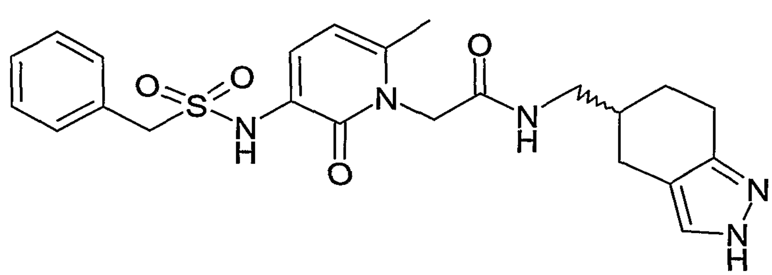
A further aspect of the invention is a process for the preparation of the novel compounds of formula I by condensation reaction.

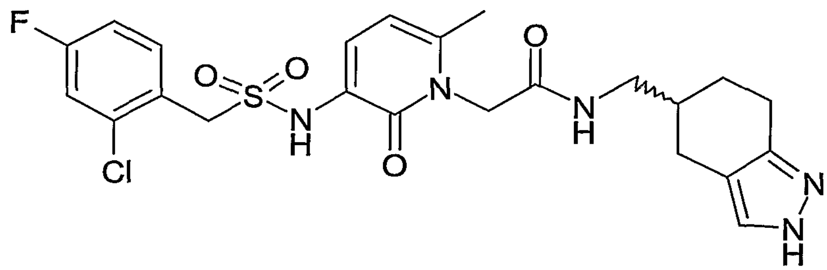
The above and further aspects to achieve the object according to the invention together with the features and effects obtained will be more obvious from the embodiments described in the following.

The compounds of the present invention have one or more stereogenic centres whose absolute configuration can be *R* or *S* and can be present in the form of racemates, racemic mixtures, pure enantiomers, mixtures of diastereomers or pure diastereomers.

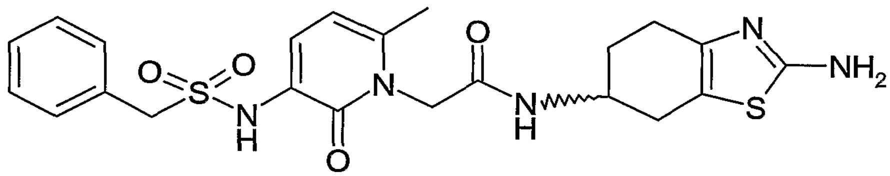
Preferred embodiments are compounds wherein W is R^1 or R^1SO_2 and wherein R^1 is $R^2(CH_2)_n$. Especially useful class of compounds is the embodiment wherein R^3 is CH_3.

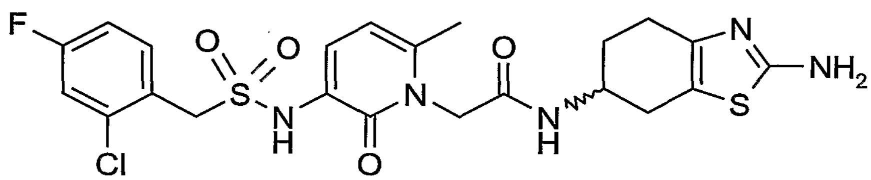
In one exemplification of the invention, W is R_1SO_2, R^3 is CH_3, B is CH_2, and A is 4,5,6,7-tetrahydroindazole attached to group B via the position 5. Specific embodiments of this class include (note that the methyl group is conventionally indicated as a single bond attached to a ring):



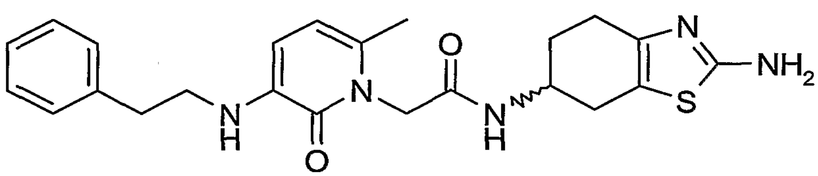


In another exemplification of the invention, W is R^1SO_2, B is $(CH_2)_k$ wherein k is 0 and A is 4,5,6,7-tetrahydro-1,3-benzothiazole attached to group B via the position 6.

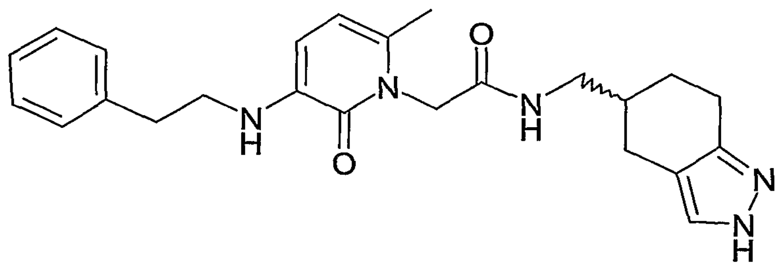




In a third exemplification of the invention, W is R^1, B is $(CH_2)_k$ wherein k is 0 and A is 4,5,6,7-tetrahydro-1,3-benzothiazole attached to group B via the position 6.



In a fourth exemplification of the invention, W is R^1, B is CH_2 and A is 4,5,6,7-tetrahydroindazole attached to group B via the position 5.



The invention also relates to the pharmaceutically acceptable salts of the compounds of formula I obtainable by treating the compounds I according to the invention with acids or bases in suitable organic solvents conventionally used in this technical field.

The pharmaceutically acceptable salts of the compounds of formula I (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, hydrobromide, hydrochloride, hydroiodide, lactate, maleate, methanesulfonate, nicitinate, nitrate, oxalate, pamoate, 3-phenylpropionate, picrate, pivalate, propionate, pectinate, succinate, sulfate, tartrate, thiocyanate, tosylate, and audecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, N-methyl-D-glucamine and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, dialkylsulfates, and diamylsulfates, long chain halides, aralkyl halides and others.

The invention further provides the use of novel compounds of the formula I for manufacturing medicaments comprising therapeutically effective ingredients. The novel compounds are thrombin inhibitors having improved activity, good bioavailability, long half-life and are capable of being orally administered. They inhibit thrombin and formation of fibrin. In particular, the compounds of the invention have a good selectivity of the thrombin inhibiting activity with respect to trypsin inhibition.

They are useful in the treatment or prevention of a variety of thrombosis forms: (i) venous thromboembolism due to formation of a thrombus within a vein (*venous thrombosis*) associated with acquired (prolonged bedrest, surgery, injury, malignancy, pregnancy and postpartum states) or inherited (deficiency of natural coagulation inhibitors) risk factors, obstruction or occlusion of a lung artery by a detached thrombus (*pulmonary embolism*), (ii) cardiogenic thromboembolism due to formation of a thrombus in the heart associated with cardiac arrhythmia, heart valve defect, prosthetic heart valves or heart disease, embolism of peripheral arteries caused by a detached thrombus, most commonly in the brain (*ischemic stroke*), (iii) arterial thrombosis due to underlying atherosclerotic processes in the arteries which obstructs or occludes an artery and causes myocardial ischemia (*angina pectoris, acute coronary syndrome*) or myocardial infarction, obstructs or occludes a peripheral artery (*ischemic peripheral artery disease*) and obstructs or occludes the artery after the procedure on the blood vessel (*reocclusion or restenosis after transluminal coronary angioplasty, reocclusion or restenosis after percutaneous transluminal angioplasty of peripheral arteries*) and (iv) in the number of states (e.g., in complications in pregnancy, in metastasing malignant diseases, after extensive injuries, in bacterial sepsis) when thrombogenic activation causes widespread formation of thrombi within the vascular system (*disseminated intravascular coagulation*).

The compounds of the present invention may be also used as an adjunct therapy in conjunction with thrombolytic therapy in recent myocardial infarction, in combination with aspirin in patients with unstable angina pectoris designed to undergo percutaneous transluminal angioplasty and in the treatment of patients with thrombosis and with heparin-induced thrombocytopenia.

The compounds of the present invention may further be used for the prevention of blood coagulation which is in contact with nonbiological surfaces (vascular prosthesis, vascular stents, prosthetic heart valves, extracorporeal circulation systems, hemodialysis) and *in vitro* to prevent coagulation in biological samples for testing or storage.

The pharmaceutical compositions comprising the compounds of the formula I according to the present invention may be formulated as injectable or oral formulations. In addition to the active ingredient they preferably contain different standard additives depending on the use. The pharmaceutical compositions can be prepared according to the standard procedures.

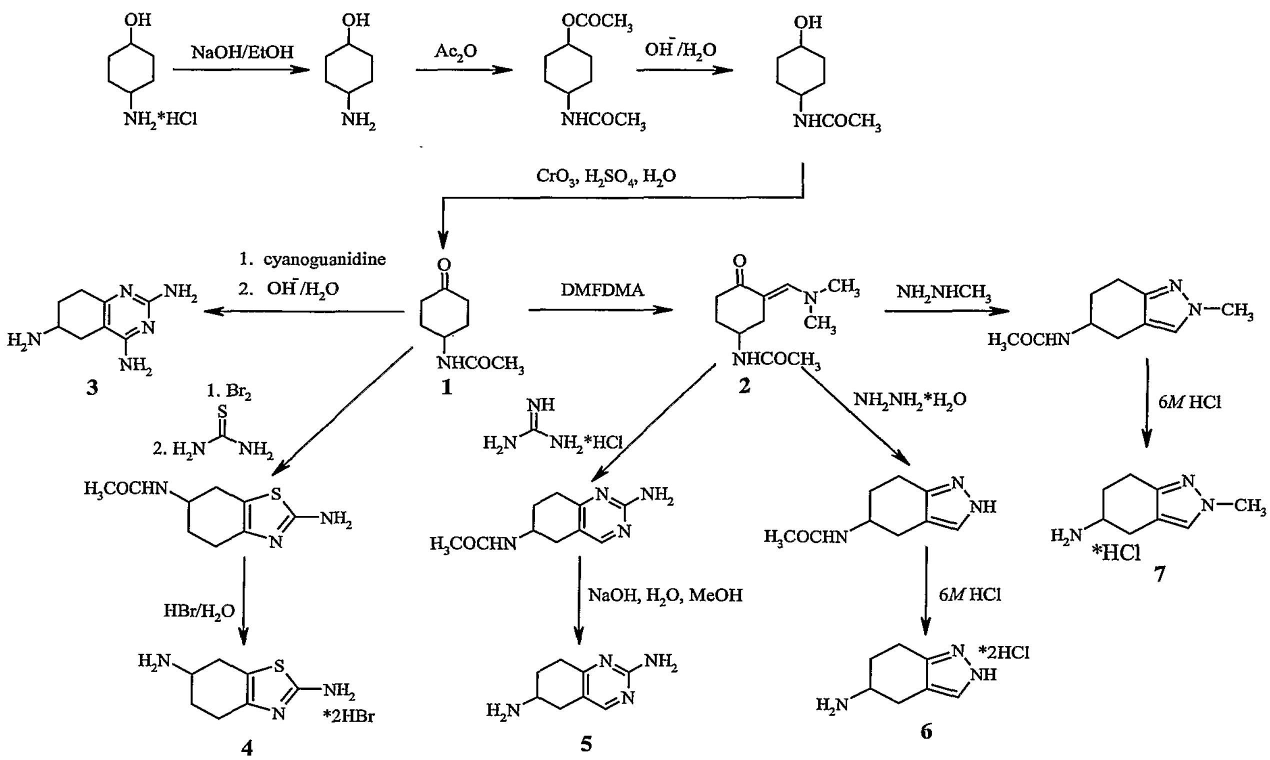
The preparation may be formulated in such a manner as to permit controlled and sustained release of the active ingredient. Dosage, frequency and mode of administration depend on a variety of factors, they also depend on individual active ingredient and its pharmacokinetic parameters and on patient's condition.

Embodiments for the processes for the preparation of compounds of general formula I according to the invention are described in the following.

The starting heterocyclic compounds are prepared as depicted in Schemes I, II and III or according to the methods described in the literature.

2,4,6-Triamino-5,6,7,8-tetrahydroquinazoline (**3**), 2,6-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole (**4**), 2,6-diamino-5,6,7,8-tetrahydroquinazoline (**5**) and 5-amino-4,5,6,7-tetrahydro-2*H*-indazole (**6**) are prepared according to the procedures described in SI patent application P-200000111 and depicted in Scheme I. 3-Amino-2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-6(2*H*)-ylamine is prepared from *N*-(4-oxocyclohexyl)acetamide (**1**) by bromination, cyclization with thiosemicarbazide and subsequent acid hydrolysis. 2-Methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-ylamine (**7**) is prepared from enaminoketone (**2**) by cyclization with *N*-methylhydrazine and subsequent acid hydrolysis (Scheme I). 4,5,6,7-Tetrahydro-2*H*-isoindol-5-amine is prepared by alkaline catalyzed reaction of enaminoketone (**2**) with glycine to the corresponding - K salt which after addition of acetanhydride is cyclized, decarboxylated and the compound formed is acetylated to suitable diamide which by subsequent basic hydrolysis is converted to the corresponding amine (Bach N. J., Kornfeld E. C., Jones N. D. et al. *J. Med. Chem.* 1980, *23*, 481).

SCHEME I



2,4,5-Triamino-5,6,7,8-tetrahydroquinazoline, 2,5-diamino-5,6,7,8-tetrahydroquinazoline, 4-amino-4,5,6,7-tetrahydro-2*H*-indazole, 4-amino-4,5,6,7-tetrahydro-2*H*-isoindole and 2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-4-ylamine are prepared from 1,3-cyclohexanedione and a suitable reagent for cyclization analogously to the procedures described in the articles: Bach N. J., Kornfeld E. C., Jones N. D. et al. *J. Med. Chem.* 1980, *23*, 481.; Modest E.J., Chatterjee S., Protopapa H.K. *J. Am. Chem. Soc.* 1965, *87*, 1837.; Gangjee A., Zaveri N., Queener S.F. et al. *J. Heterocyclic Chem*, 1995, *32*, 243 and subsequent conversion of the keto group into the amino group, for example by reductive amination (Abdel-Magid A. F., Carson K. G., Harris B. D. et al. *J. Org. Chem.* 1996, *61*, 3849).

2,7-Diamino-4,5,6,7-tetrahydro-1,3-benzothiazole, 2,4-diamino-4,5,6,7-tetrahydro-1,3-benzothiazole, 2,4,8-triamino-5,6,7,8-tetrahydroquinazoline, 2,8-diamino-5,6,7,8-tetrahydroquinazoline, 7-amino-4,5,6,7-tetrahydro-2*H*-indazole, 7-amino-4,5,6,7-tetrahydro-2*H*-isoindole, 2,6-diamino-1,3-benzothiazole, 2,5-diamino-4,5,6,7-tetrahydro-1*H*-benzimidazole, 2,4-diamino-4,5,6,7-tetrahydro-*1H*-benzimidazole, 2,6-diamino-4,5,6,7-

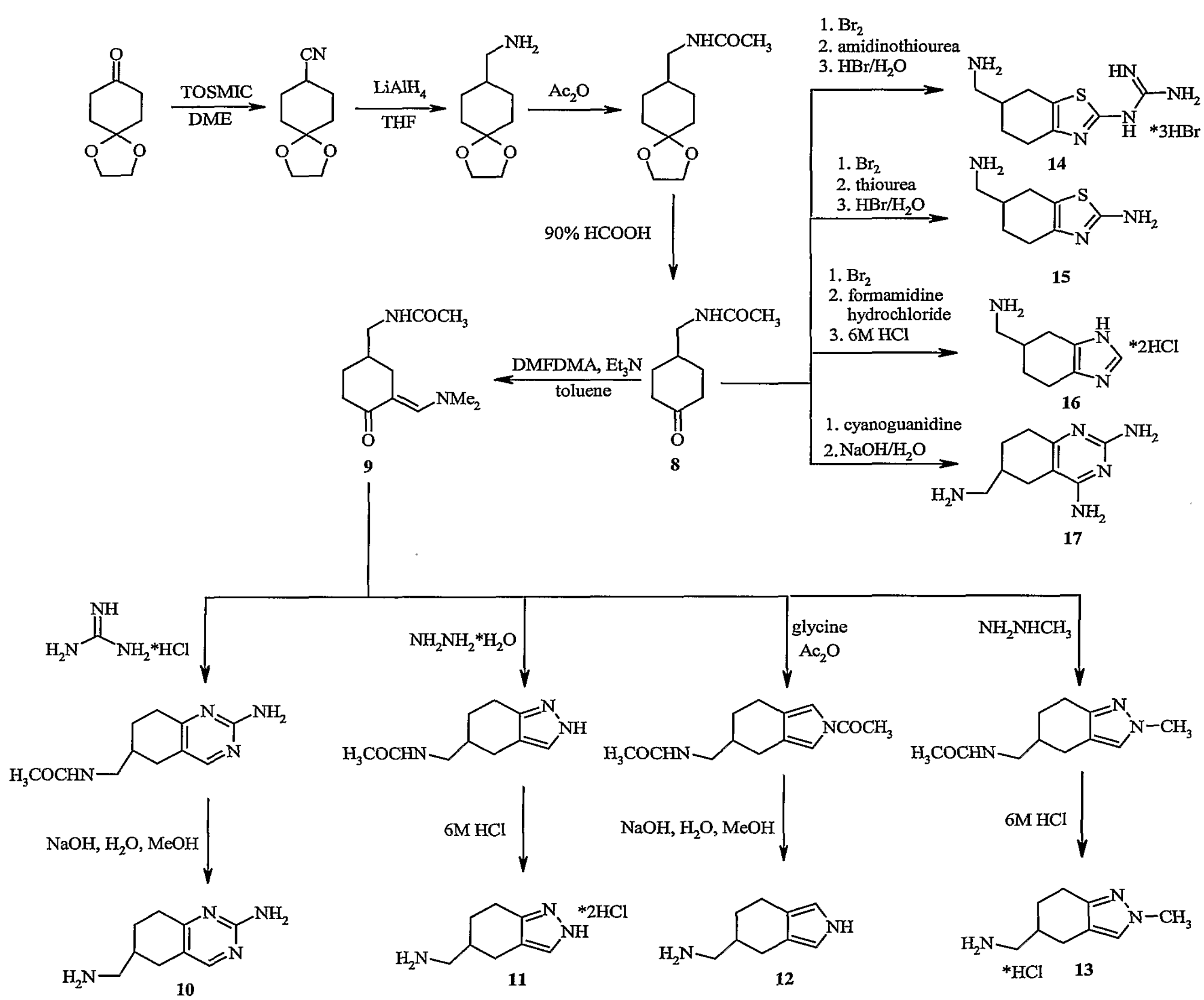
tetrahydro-1,3-benzoxazole, and 2,4-diamino-4,5,6,7-tetrahydro-1,3-benzoxazole are prepared according to the procedures described in SI patent application no. P-200000111.

Starting from cyclopentane-1,3-dione, cyclopentan-1,3-dione monoethylene acetal and *N*-(3-oxocyclopentyl)acetamide according to analogous procedures as described in SI patent application no. P-200000111, the amino derivatives of 6,7-dihydro-5*H*-cyclopenta[*d*] pyrimidine, 1,4,5,6-tetrahydrocyclopenta[*d*]imidazole, 5,6-dihydro-4*H*-cyclopenta[*d*][1,3] thiazole, 5,6-dihydro-4*H*-cyclopenta[*d*][1,3]oxazole, 2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole, 2,4,5,6-tetrahydrocyclopenta-[*c*]pyrazole and 5,6-dihydro-4*H*-cyclopenta[*d*]imidazole are prepared.

As depicted in Scheme II and described in SI patent application no. P-200000111, 6-(aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine (**10**) (Peterlin-Mašič, L.; Kikelj, D. *Tetrahedron Lett.* 2000, *41*, 5589), 4,5,6,7-tetrahydro-2*H*-isoindol-5-ylmethanamine (**12**), 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine (**11**) (Peterlin-Mašič, L.; Kikelj, D. *Tetrahedron Lett.* 2000, *41*, 5589), 6-(aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine (**15**) and 6-(aminomethyl)-5,6,7,8-tetrahydro-2,4-quinazolinediamine (**17**) are prepared. 2-Methyl-4,5,6,7-tetrahydro-2*H*-indazole-5-yl)methanamine (**13**) is prepared from enaminoketone (**9**) by cyclization with *N*-metylhydrazine and subsequent acid hydrolysis (Scheme II). *N*-[6-(Aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl]guanidine (**14**) is prepared from ketone (**8**) by cyclization with amidinothiourea and subsequent acid hydrolysis. According to the analogous procedure 4,5,6,7-tetrahydro-1*H*-benzimidazole-6-ylmethanamine (**16**) is prepared from (**8**) and formamidine hydrochloride (Scheme II). 3-Amino-2-imino-4,5,6,7-tetrahydro-1,3-benzothiazol-6(2*H*)-ylmethylamine is prepared from *N*-[(4-oxocyclohexyl)methyl]acetamide (**8**) by bromination, cyclization with thiosemicarbazide and subsequent acid hydrolysis.

4-(Aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine, 4,5,6,7-tetrahydro-2*H*-isoindol-7-ylmethanamine, 4,5,6,7-tetrahydro-2*H*-indazol-7-ylmethanamine, 8-(aminomethyl)-5,6,7,8-tetrahydro-2,4-quinazolinediamine and 8-(aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine are prepared according to the procedures described in SI patent application no. P-200000111.

SCHEME II

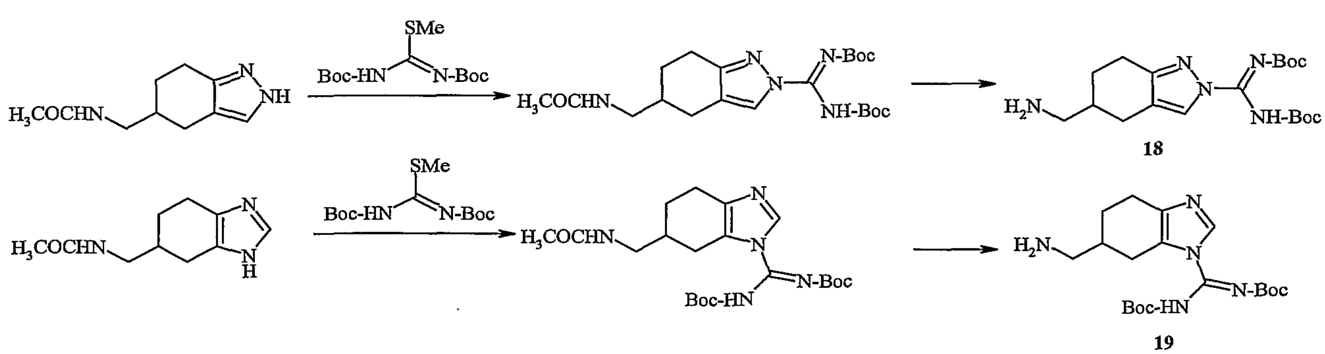


Starting from cyclopentane-1,3-dione, cyclopentane-1,3-dione monoethylene acetal and *N*-(3-oxocyclopentyl)acetamide according to the analogous procedures as described in SI patent application no. P-200000111 and depicted in Scheme II, aminomethyl derivatives of 6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine, 1,4,5,6-tetrahydrocyclopenta[*d*]imidazole, 5,6-dihydro-4*H*-cyclopenta-[*d*][1,3]thiazole, 5,6-dihydro-4*H*-cyclopenta[*d*][1,3]oxazole, 2,4,5,6-tetrahydrocyclopenta[*c*]pyrrole, 2,4,5,6-tetrahydrocyclopenta[*c*]pyrazole and 5,6-dihydro-4*H*-cyclopenta[*d*]imidazole are prepared.

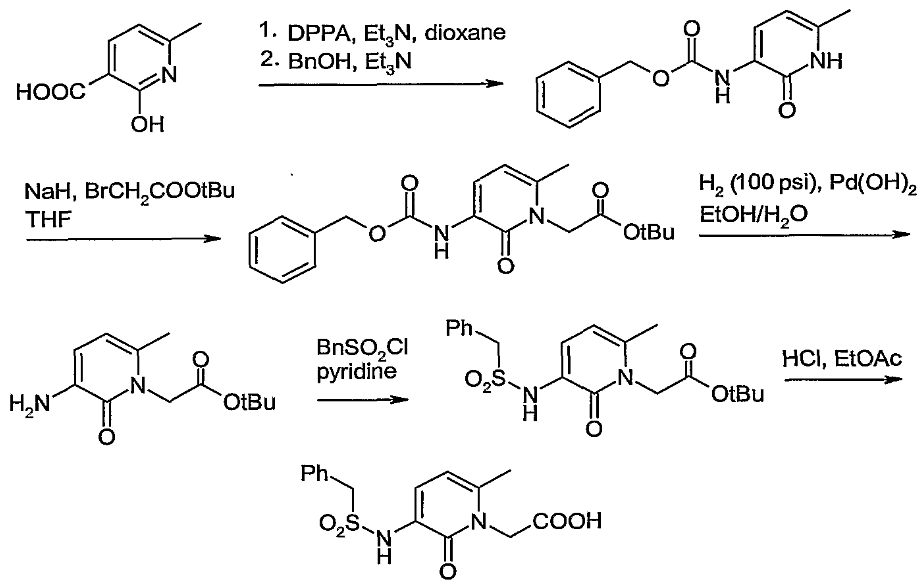
6-(Aminomethyl)-4-quinazolinamine, 7-(aminomethyl)-4-quinazolinamine, 6-(aminomethyl)-2-quinazolinamine, 7-(aminomethyl)-2-quinazolinamine, 6-(aminomethyl)-2,4-quinazolinediamine and 7-(aminomethyl)-2,4-quinazolinediamine are prepared from 6-(bromomethyl)-4-chloroquinazoline, 7-(bromomethyl)-4-chloroquinazoline, 6-(bromomethyl)-2-chloroquinazoline, 7-(bromomethyl)-2-chloroquinazoline, 6-(bromomethyl)-2,4-dichloroquinazoline or 7-(bromomethyl)-2,4-dichloroquinazoline and ammonia in polar organic solvents at increased pressure and elevated temperature. The above 6-bromomethyl- and 7-(bromomethyl)chloroquinazolines are prepared by bromination of 6-methyl-4-chloroquinazoline, 6-methyl-2-chloroquinazoline, 7-methyl-4-chloroquinazoline, 7-methyl-2-chloroquinazoline, 6-methyl-2,4-dichloroquinazoline and 7-methyl-2,4-dichloroquinazoline according to the procedure as, for example, described for the preparation of 6-bromomethyl-4-chloroquinazioline in EP 566226 and in SI patent application no. P-200000111.

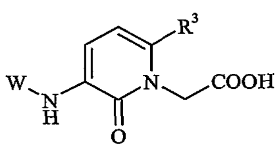
tert-Butyl {6-[(acetylamino)methyl]-4,5,6,7-tetrahydro-1*H*-benzimidazol-1-yl}[(*tert*-butoxy-carbonyl)amino]methylidenecarbamate (**18**) and *tert*-butyl{6-[(acetylamino)methyl]-4,5,6,7-tetrahydro-1*H*-benzimidazol-1-yl}[(*tert*-butoxycarbonyl)amino]methylidenecarmabate (**19**) are prepared as disclosed in Scheme III from suitable tetrahydroindazole and tetrahydrobenzimidazole- derivative, respectively with *N,N*-di-(Boc)-*S*-methylisothiourea according to the analogous procedure as described in the article Nicholau K.C. et al. *Bioorg. Med. Chem. Lett.* 1998, *6*, 1185 and subsequent alkaline hydrolysis of the acetamide group.

SCHEME III



SCHEME IV

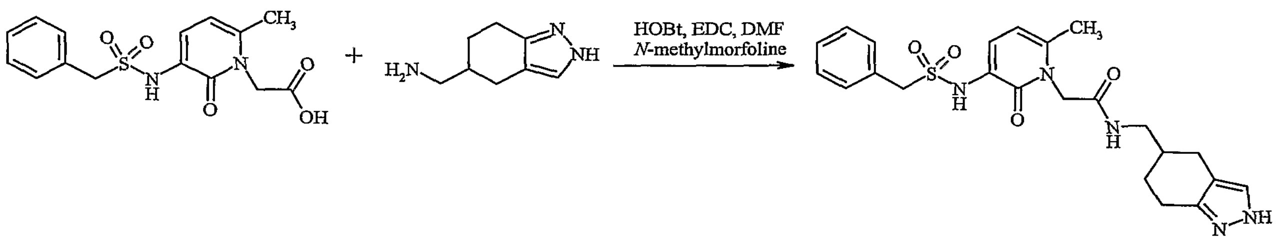


Fragments  from general formula (I) are prepared as depicted in Scheme IV (for example wherein R^3 is methyl and W is benzylsulfonyl) and described in patent application WO 9701338. The starting compound 6-methyl-2-hydroxypyridinecarboxylic acid is converted with benzyl alcohol in the presence of DPPA into carbamate. Protected pyrimidone is alkylated with *t*-butylbromoacetate in the presence of a base. Then the Cbz group is removed by catalytic hydrogenation. The obtained amine reacts with suitable reagents, in our example with benzylsulfonyl chloride in the presence of pyridine. Finally, the Boc protective group is removed under the acidic conditions.

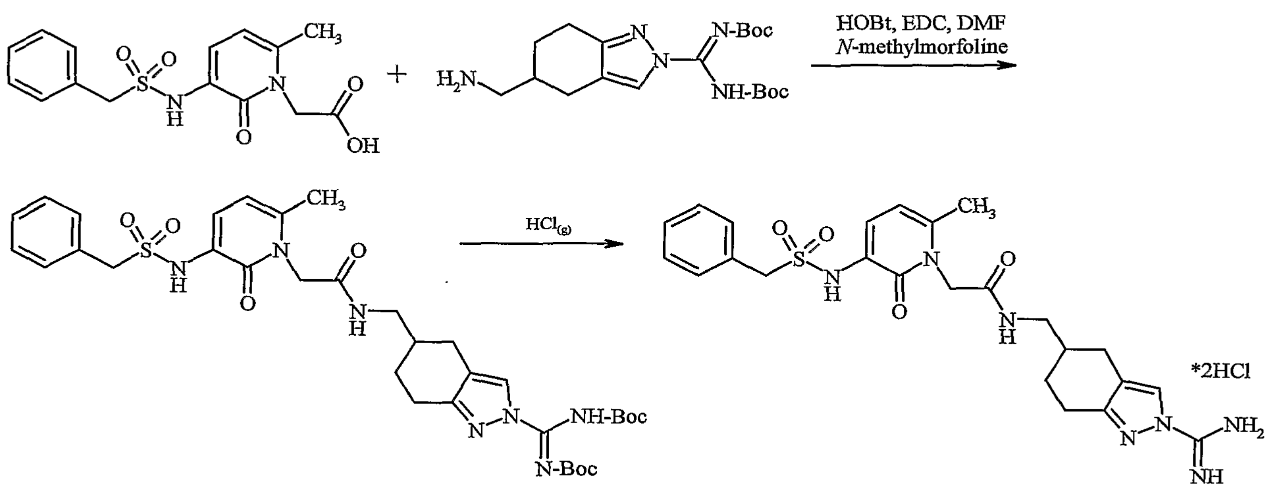
Using suitably substituted starting compounds and reagents in individual reaction steps, the compounds with suitable W and R^3 groups can be analogously prepared. For example, pyridinone substituted at position 6 with ethyl, isopropyl, cyclopropyl or similar group, can be used as a starting compound to obtain compounds with different R^3 substituents. Compounds with different W fragments, wherein W is R^1, R^1OCO, R^1CO, R^1SO_2 or $(R^1(CH_2)_n)_mNCO$, can be prepared by using suitable reagents for alkylation, acylation,

sulfonation and carbamoylation such as, for example, alkyl halides, alkoxycarbonyl halides, acyl halides or alkyl isocynates in the second step of synthesis.

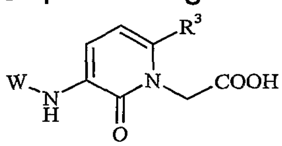
SCHEME V



SCHEME VI



Compounds of general formula (I) are prepared by condensation of fragment



(Scheme IV) with fragment A-B-NH_2 (Schemes I-III) as presented in Schemes V and VI. For condensation, conventional reagents may be used for formation of the peptide bond as, for example, dicyclohexyl carbodiimide, EDC, HOBt, DPPA or chloroformates, etc. (see, for example, Bodanszky M., Bodanszky A. *The Practice of Peptide Synthesis,* Springer, Berlin,

1994). For the removal of protecting groups, as presented for example in Scheme VI, generally known procedures can be used as described, for examples, in the books: (Green T.W. *Protecive groups in organic synthesis,* John Wiley § Sons, New York, 1980; Kocienski P. J. *Protecting groups*, Thieme Verlag, Stuttgart, 1994).

Pharmaceutically acceptable salts of the compounds of formula I are prepared by treating the compounds I with acids or bases in suitable organic solvents conventionally used in this technical field.

BIOLOGICAL TESTS

I. Enzyme assay for determination of the activity of thrombin inhibitors

1. Principle

Thrombin cleaves amide bonds in a synthetic chromogenic substrate whereby brown coloured p-nitroaniline (p-NA) is released. The amount of p-NA produced is directly proportionate to the absorbance measured at a wavelength of 405 nm using a spectrophotometer. When thrombin inhibitor is added, the amidolytic activity of the enzyme decreases. The potency of the inhibitor is expressed by the inhibition constant (K_i).

2. Reagents

Thrombin (human thrombin, 308 NIH units, Sigma): the contents of the vial are dissolved in distilled water to give a stock solution of 20 NIH units/ml. The stock solution is pipetted into 0.5 mL aliquots and stored at -70°C. Immediately before use a working solution of thrombin of NIH units/mL activity is prepared with HBSA buffer. The final concentration of thrombin in a microtiter plate is 0.5 NIH units/mL.

Chromogenic substrate for thrombin (S-2238, Chromogenix, 25 mg). 1 mM substrate solution is prepared, pipetted into 0.5 mL aliquots and stored at -20°C. Before use, 160 and 80 μM substrate solutions of the substrate are prepared with distilled water. The final concentrations of the substrate in the reaction mixture are 40 and 20 μM (K_m = 2.6 μM), respectively.

HBSA buffer, pH 7.5: 10 mM Hepes buffer (HEPES, Sigma), 150 mM NaCl and 0.1% (w/v) bovine serum albumin (98% bovine serum albumin, Sigma) are dissolved in bidistilled

water. The pH is adjusted with 0.1 M NaOH solution.

Inhibitors are dissolved in DMSO to give a 10 mM stock solution. Working solutions (final concentrations within the range 10 to 100 μM) are prepared with distilled water. The highest concentration of DMSO in a microtiter plate does not exceed 3%.

3. Procedure

Measurements are carried out in the microtiter plate. 50 μL HBSA buffer, 50 μL inhibitor solution of different concentrations (for control 50 μL HBSA buffer) and 50 μL of thrombin solution are pipetted into the wells of a microtiter plate. The plate is incubated at a temperature of 25°C for 15 minutes. After incubation 50 μL of the chromogenic substrate is added and the microtiter plate is placed in the spectrophotometer (Tecan, Sunrise). The absorbance increase at 405 nM is measured at 10-second intervals for a period of 15 minutes at a temperature of 25°C.

For determination of the inhibition constant (K_i) 40 and 20 μM substrate is used. Each measurement is carried out in triplicate and the result is the averaged value of three measurements.

4. Determination of the inhibition constant (K_i)

K_i is determined according to the principle, described by Cheng and Prusoff (Biochem Pharmacol, 1973, 22, 3099). Initial velocities of the reaction in the presence and absence of the inhibitor are measured. The change in the absorbance in the time unit (*v*) is calculated from the initial, linear part of the reaction. For competitive inhibitors it holds that

$$\frac{v_i}{v_0} = \frac{K_m + S}{K_m \cdot (1 + (I/K_i)) + S}$$

and it follows that

$$K_i = \frac{I}{((S/K_m) + 1) \cdot ((v_0/v_i) - 1)}$$

I = inhibitor concentration, S = substrate concentration, K_m = Michaelis constant, v_o = initial velocity of the reaction in the absence of inhibitor, v_i = initial velocity of the reaction in the presence of inhibitor.

Measurements are carried out with two concentrations of the inhibitor and two concentrations of the substrate. For each combination of the used concentrations of the substrate and the inhibitor, K_i is calculated and the result is their averaged value.

II. Determination of selectivity of the inhibitor activity against thrombin with respect to trypsin inhibition

1. Principle

Because thrombin and trypsin are closely related with respect to the specificity against the substrate due to comparable structure of the active site, the selectivity of inhibitory activity against thrombin is determined with respect to trypsin inhibition which is a nonspecific serine protease. The inhibitory activity against thrombin is determined as described above. Trypsin inhibition is measured in the same manner as in determination of inhibitory activity for thrombin except that a different chromogenic substrate is used. For both enzymes K_i is calculated. Selectivity of the inhibitor is expressed as a ratio of K_i for trypsin to K_i for thrombin.

2. Reagents

Trypsin (bovine, 6000 BAEE Units/mg protein, Sigma): A stock solution of trypsin with the activity of 300 U/mL is prepared, pipetted into 0.2 mL aliquots and stored at -70°C. Immediately before use, the stock solution is thawed and a working solution of 4 mU/mL is prepared with HBSA buffer. The final trypsin activity in a microtiter plate is 1 mU/mL.

Chromogenic substrate for trypsin (S-2222, Chromogenix, 25 mg): 2 mM substrate solution is prepared, pipetted into 0.3 mL aliquots and stored at -20°C. Before use the stock solution is thawed and 400 and 200 μM substrate solutions are prepared The final concentrations of the substrate in the reaction mixture are 100 and 50 μM. (K_m = 25 μM)

HBSA buffer, pH 7.5: 10 mM Hepes buffer (HEPES, Sigma), 150 mM NaCl and 0.1% (w/v) bovine serum albumin (98% bovine serum albumin, Sigma) are dissolved in bidistilled water. The pH is adjusted with 0.1M NaOH solution.

Inhibitors are dissolved in DMSO to give a 10 mM stock solution. Working solutions (final concentrations in the range from 10 to 600 μM) are prepared with distilled water. The highest concentration of DMSO in a microtiter plate does not exceed 10%.

For determination of K_i 100 and 50 μM substrate is used. Each measurement is carried out in triplicate and the result is the averaged value of three measurements.

3. Procedure

The procedure is the same as the procedure described for determination of the inhibitory activity against thrombin. The concentrations of the reagents described for determination of the inhibitory activity with respect to trypsin are used.

4. Determination of the inhibition constant (K_i)

It is determined in the same manner as determination of K_i for thrombin.

5. Determination of the selectivity

K_i for thrombin and K_i for trypsin are determined. The selectivity is defined as the ratio:

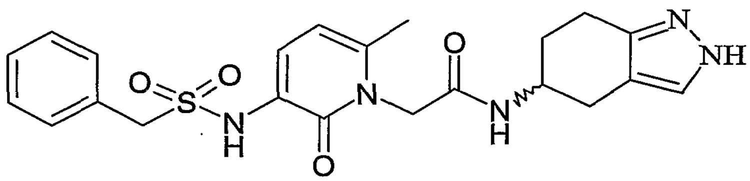
$$\text{selectivity} = \frac{K_i\,(\text{trypsin})}{K_i\,(\text{thrombin})}$$

ABBREVIATIONS

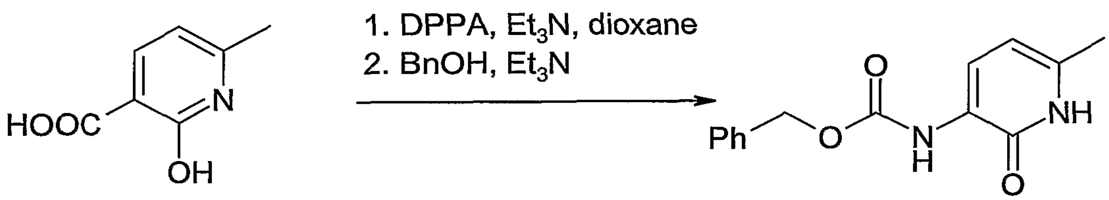
Boc	*tert*-butyloxycarbonyl
Cbz	Benzyloxycarbonyl
HOBt	1-hydroxy benzotriazole hydrate
EDC	*N'*-(3-dimethylaminopropyl)-*N*-ethyl-carnodiimide hydrochloride
DPPA	Diphenylphosphorylazide
DMF	*N,N*-dimethylformamide
Et_3N	Triethylamine
EtOH	Ethanol
MeOH	Methanol
THF	Tetrahydrofuran
EtOAc	Ethylacetate

The invention is illustrated but in no way limited by the following examples:

EXAMPLE 1: Synthesis of (±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]-*N*-[(4,5,6,7-tetrahydro-2*H*-indazole-5-yl]acetamide



STEP 1: Synthesis of 3-benzyloxycarbonylamino-6-methyl-2-pyridinone



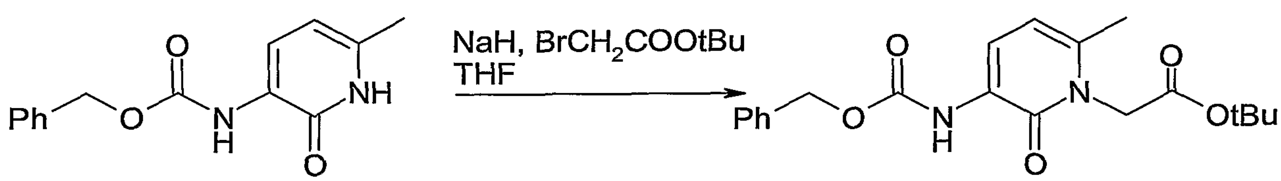
DPPA (8.5 mL, 39.2 mmol) was added to a stirred mixture of 2-hydroxy-6-methylpyridine-3-carboxylic acid (6.00 g, 39.2 mmol) and triethylamine (5.5 mL, 39.2 mmol) in anhydrous dioxane (72 mL) and the resulting solution was refluxed for 16 hours. Triethylamine (5.5 mL, 39.2 mmol) and benzyl alcohol (4.2 mL, 36.8 mmol) were added and the solution was refluxed for further 24 hours. The reaction mixture was concentrated *in vacuo*. To the residue were added dichloromethane (130 mL) and saturated NaCl solution and the mixture was acidified with 1*M* HCl to p*H* = 1 (43 mL). The water phase was extracted with dichloromethane twice; the combined organic phases were washed with saturated $NaHCO_3$ solution, saturated NaCl solution and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the product was recrystallized from methanol to give 4.95 g (19,2 mmol) of the solid brown compound.

η = 49 %

T_{tal} = 178-179°C

3-benzyloxycarbonylamino-6-methyl-2-pyridonone	
ANALYSIS	RESULTS
IR (KBr)	$\nu[cm^{-1}]$ = 3390, 2798, 1730, 1647, 1522, 1471, 1201, 1042, 753, 698
MS (EI)	m/z (%) = 258 (M^+, 25), 91 (100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 2.32 (s, 3H, CH_3), 5.23 (s, 2H, $PhCH_2$), 6.09 (d, 1H, *J* = 7.53 Hz, pyridinone H-5), 7.34-7.46 (m, 5H, Ph), 7.69 (broad s, 1H, NHCOO), 8.07 (d, 1H, *J* = 7.16 Hz, pyridinone H-4).

STEP 2: Synthesis of *tert*-butyl 2-[3-{[(benzyloxy)carbonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate



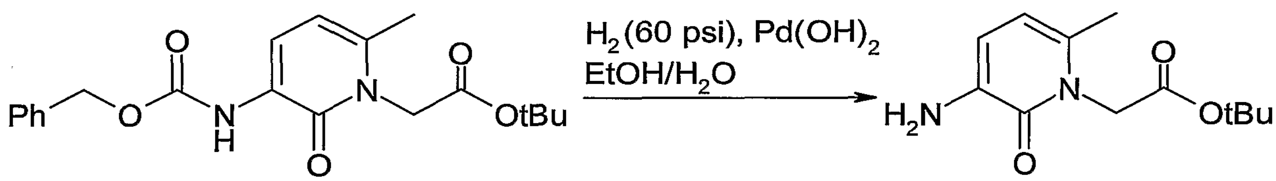
A mixture of 3-benzyloxycarbonylamino-6-methyl-2-pyridinone (4.91 g, 19.0 mmol) in anhydrous THF (50 mL) was cooled to 0°C and NaH (0.50 g, 20.9 mmol) was added while stirring. To the resulting solution was added *t*-Bu-bromoacetate (4.3 mL, 25.7 mmol) and after several minutes the precipitate formed. While stirring the reaction mixture was slowly warmed to room temperature. After 3 hours the solvent was evaporated under reduced pressure, 1:1 water/saturated NaCl solution (20 mL) was added to the residue and extracted with 6:1 THF/CH_2Cl_2 (65 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Hexane was added to this solid product and filtered to give 6.19 g (16.6 mmol) of the brown-grey solid compound.

η = 87%

T_{tal} = 127-130°C

tert-butyl 2-[3-{[(benzyloxy)carbonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate	
ANALYSIS	RESULT
IR (KBr)	ν[cm^{-1}] = 3234, 2954, 1748, 1718, 1654, 1530, 1366, 1219, 1149, 1058, 974, 778, 567
MS (EI)	m/z (%) = 372 (M^+, 33), 91 (100)
NMR CDCl$_3$, 300 MHz	δ[ppm] = 1.49 (s, 9H, *t*-Bu), 2.27 (s, 3H, CH_3), 4.76 (s, 2H, $PhCH_2$), 5.21 (s, 2H, NCH_2), 6.11 (d, 1H, *J* = 8.29 Hz, pyridinone H-5), 7.32-7.40 (m, 5H, Ph), 7.77 (broad s, 1H, NHCOO), 7.96 (d, 1H, *J* = 7.92 Hz, pyridinone H-4).

STEP 3: Synthesis of *tert*-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate



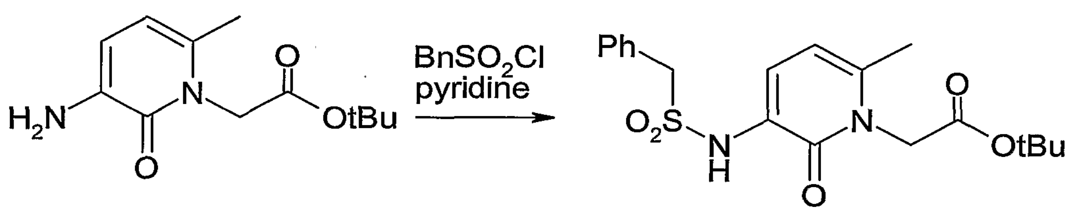
To *tert*-butyl 2-[3-{[(benzyloxy)carbonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (6.19 g, 16.6 mmol) in the reactor a mixture of 4:1 ethanol/water (77 mL) was added and degassed with argon for several minutes. During degassing $Pd(OH)_2$ (0.613 g) was added and subjected to catalytic hydrogenation in the reactor containing a hydrogenating agent under the conditions: $p(H_2)$ = 100 psi, t = 2 h. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure. To obtain a solid ethanol was added to the resulting material several times and the azeotropic mixture with water was distilled under reduced pressure to give 3.18 g (13.4 mmol) of a grey compound.

η = 79%

T_{tal} = 97-100°C

tert-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate	
ANALYSIS	RESULT
IR (KBr)	ν[cm^{-1}] = 3434, 3324, 2976, 1746, 1649, 1595, 1357, 1233, 1152, 785
MS (EI)	m/z (%) = 238 (M^+, 25), 182 (100)
NMR CDCl$_3$, 300 MHz	δ[ppm] =1.50 (s, 9H, *t*-Bu), 2.21 (s, 3H, CH_3), 4.06 (broad s, 2H, NH_2), 4.78 (s, 2H, NCH_2), 5.93 (d, 1H, *J* = 7.16 Hz, pyridinone H-5), 6.51 (d, 1H, *J* = 7.16 Hz, pyridinone H-4).

STEP 4: Synthesis of *tert*-butyl 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate



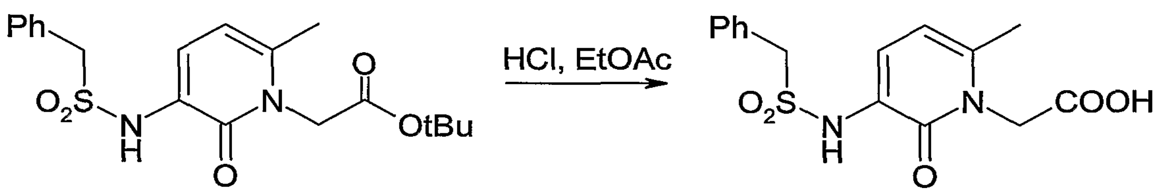
To a solution of *tert*-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (3.04 g, 12.1 mmol) in pyridine (30 mL) cooled to 0°C was added benzylsulfonylchloride (2.67 g, 15.1 mmol). While stirring of the reaction mixture the precipitate formed. After one hour the solvent was evaporated under reduced pressure and the product was partitioned between dichloromethane and 10% $KHSO_4$ solution. The aqueous phase was extracted with dichloromethane twice. The combined organic phases were dried over a drying agent and the solvent was evaporated under reduced pressure. A brown-reddish product obtained was suspended in ethyl acetate and heated to reflux, then cooled and filtered to give 2.56 g (6.52 mmol) of a pink product.

η = 51%

T_{tal} = 177-180°C

tert-butyl 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3149, 1740, 1652, 1598, 1454, 1365, 1230, 1137, 887, 771, 540
MS (EI)	m/z (%) = 392 (M^+, 35), 181 (100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 1.53 (s, 9H, *t*-Bu), 2.28 (s, 3H, CH_3), 4.33 (s, 2H, $PhCH_2$), 4.77 (s, 2H, NCH_2), 6.03 (d, 1H, *J* = 7.54 Hz, pyridinone H-5), 7.22-7.36 (m, 7H, Ph, pyridinone H-4, SO_2NH).

STEP 5: Synthesis of 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid



HCl gas was bubbled at 0°C into a stirred suspension of *tert*-butyl 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (2.32 g, 5.91 mmol) in ethylacetate until the solution was completed. The HCl-saturated solution was stirred for further one hour at room temperature to form the thick precipitate. The product was collected by filtration to give 1.95 g (5.80 mmol) of a pale pink compound.

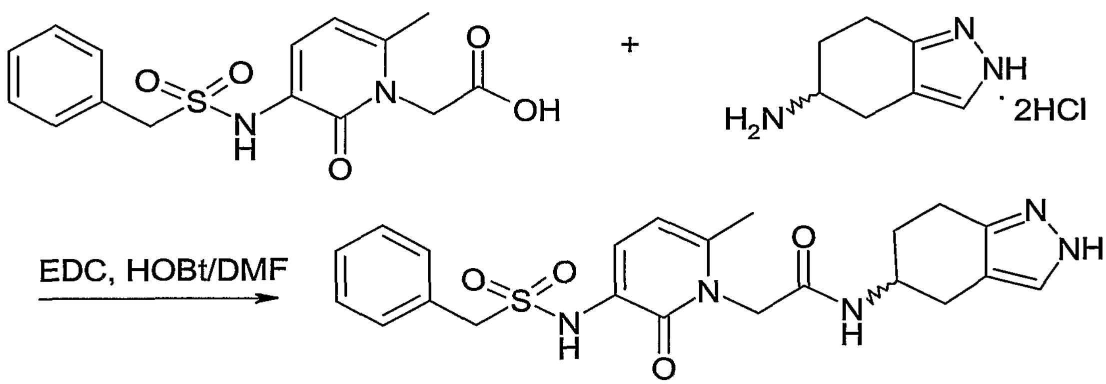
η = 98%

T_{tal} = 184-187°C

2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3145, 1713, 1654, 1601, 1457, 1368, 1258, 1150, 1030, 877, 698, 540
MS (EI)	m/z (%) = 336 (M^+, 30), 91 (100)

NMR $CDCl_3$, 300 MHz	δ[ppm] = 2.27 (s, 3H, CH_3), 4.52 (s, 2H, $PhCH_2$), 4.78 (s, 2H, NCH_2), 6.10 (d, 1H, *J* = 8.29 Hz, pyridinone H-5), 7.13 (d, 1H, *J* = 7.54 Hz, pyridinone H-4), 7.31-7.37 (m, 5H, Ph), 8.63 (s, 1H, $NHSO_2$).

STEP 6: Synthesis of (±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-yl)acetamide

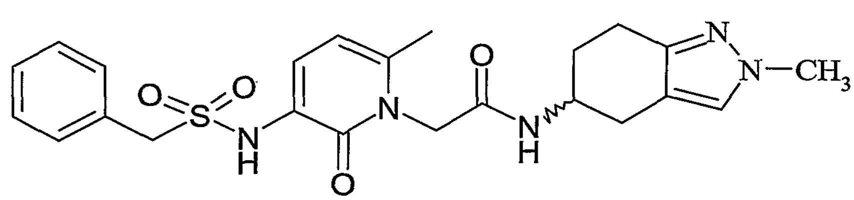


To a solution of 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid (94.1 mg, 0.28 mmol) and 4,5,6,7-tetrahydro-2*H*-indazol-5-ylamine dihydrochloride (58.8 mg, 0.28 mmol) in 1 mL of DMF was added HOBt (42.8 mg, 0.28 mmol). The pH of the solution was adjusted to 8 with *N*-methylmorpholine and EDC (53.7 mg, 0.28 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and ethylacetate and saturated $NaHCO_3$ solution were added to the residue. The water phase was extracted with ethyl acetate three times, and the combined organic phases were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The product was purified by column chromatography (silicagel, eluant CH_2Cl_2/MeOH = 9/1) to give 48 mg (38 %) of a white solid compound.

η = 38 %
T_{tal} = 187-190°C

(±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-yl)acetamide			
ANALYSIS	RESULTS		
IR (KBr)	ν[cm^{-1}] = 3290, 2936, 1652, 1567, 1445, 1360, 1154, 879, 694, 546		
MS (FAB)	m/z (%) = 456 (MH^+, 53), 154 (100)		
NMR, $DMSO-d_6$, 300 MHz	δ[ppm] = 1.71-1.81, 1.87-1.98, 2.34-2.45, 2,57-2,85 (4×m, 6H, 4-CH_2, 6-CH_2, 7-CH_2), 2.25 (s, 3H, CH_3-6'), 3.90-4.04 (m, 1H, CH-5), 4.51 (s, 2H, $PhCH_2$), 4.72 (s, 2H, NCH_2), 6.08 (d, 1H, *J* = 7.54 Hz, CH-5'), 7.12 (d, 1H, *J* = 7.53 Hz, CH-4'), 7.32-7.37 (m, 5H, Ph), 7.96 (s, 1H, CH-3), 8.32 (d, 1H, *J* = 7.16 Hz, CONH), 8.53 (broad s, 1H, SO_2NH), 12.31 (broad s, 1H, NH-2)		
CHN for $C_{22}H_{25}N_5O_4S\times$ 0.5 H_2O		Calculated	Found
	% C	56.88 %	57.07
	% H	5.64 %	5.54
	% N	15.08 %	14.84

EXAMPLE 2: Synthesis of (±)-2-[3-[(benzylsulfonyl)amino]-6-metyl-2-oxo-1(2*H*)pyridinyl]-*N*-(2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)acetamide



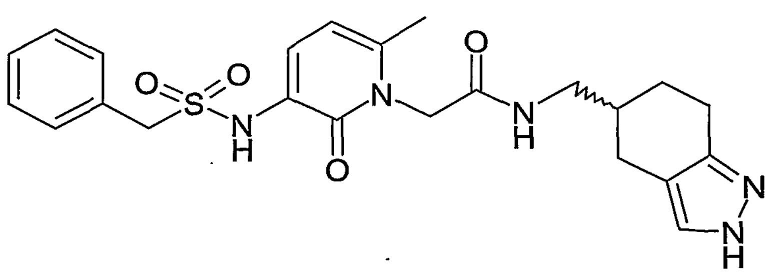
The title compound was prepared from 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-ylamine hydrochloride using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a faint yellow solid compound.

η = 63 %

T_{tal} = 203-208°C

(±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)pyridinyl]-*N*-(2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)acetamide			
ANALYSIS	RESULTS		
IR (KBr)	$\nu[cm^{-1}]$ = 3311, 3129, 2934, 1657, 1608, 1536, 1455, 1366, 1222, 1140, 1023, 882, 791, 696, 541		
MS (FAB)	m/z (%) = 470 (MH^+, 100)		
NMR CDCl₃, 300 MHz	δ[ppm] = 1.87-2.05, 2.48-2.56, 2.73-2.80, 2.88-2.95 (4×m, 6H, CH_2-4, CH_2-6, CH_2-7), 2.45 (s, 3H, CH_3-6'), 3.83 (s, 3H, CH_3-2), 4.15-4.25 (m, 1H, CH-5), 4.29 (s, 2H, $PhCH_2$), 4.50 (s, 2H, NCH_2), 6.07 (d, 1H, *J* = 7.91 Hz, CH-5'), 6.80 (d, 1H, *J* = 7.53 Hz, CONH), 7.05 (s, 1H, CH-3), 7.21-7.37 (m, 6H, Ph, SO_2NH), 7.37 (d, 1H, *J* = 7.91 Hz, CH-4').		
CHN for $C_{23}H_{27}N_5O_4S$		Calculated	Found
	% C	58.83 %	58.80 %
	% H	5.80 %	5.79 %
	% N	14.91 %	14.58 %

EXAMPLE 3: Synthesis of (±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide



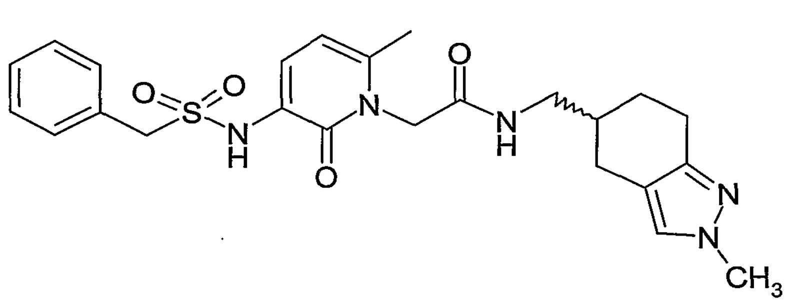
The title compound was prepared from 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine dihydrochloride using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid compound.

η = 62 %

T_{tal} = 105-107°C

(±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide			
ANALYSIS	RESULTS		
IR (KBr)	ν[cm^{-1}] = 3302, 2925, 1649, 1569, 1445, 1361, 1152, 768, 541		
MS (FAB)	m/z (%) = 470 (MH^+, 100)		
NMR $CDCl_3$, 300 MHz	δ[ppm] = 1.42-1.56 (m, 1H, CH-5), 1.88-2.01 (m, 2H, CH_2-6), 2.17-2.26, 2.51-2.61, 2.65-2.78 (3×m, 4H, CH_2-4, CH_2-7), 2.46 (s, 3H, CH_3-6'), 3.21-3.38 (m, 2H, CONHC*H*$_2$), 4.29 (s, 2H, $PhCH_2$), 4.54 (s, 2H, NCH_2), 6.08 (d, 1H, *J* = 7.92 Hz, CH-5'), 7.12-7.29 (m, 7H, Ph, SO_2NH, CONH), 7.39 (d, 1H, *J* = 7.54 Hz, CH-4'), 8.03 (broad s, 1H, CH-3).		
CHN for $C_{23}H_{27}N_5O_4S$ × 0.5 H_2O		Calculated '	Found
	% C	57.72 %	57.64 %
	% H	5.90 %	5.93 %
	% N	14.63 %	14.23 %

EXAMPLE 4: Synthesis of (±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)pyridinyl]-*N*-[(2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)methyl]acetamide



The title compound was prepared from 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine hydrochloride using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a faint

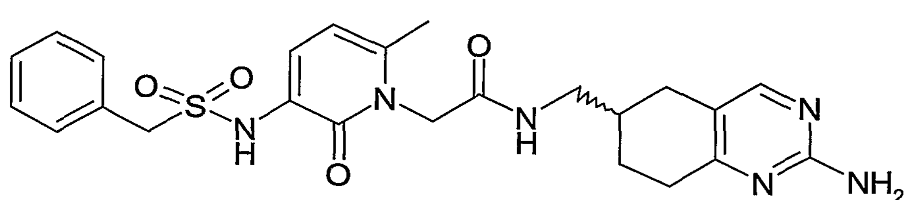
yellow solid compound.

η = 64 %

T_{tal} = 105-107°C

(±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)pyiridinyl]-*N*-[(2-methyl-4,5,6,7-tetrahydro-2*H*-indazol-5-yl)methyl]acetamide			
ANALYSIS	RESULTS		
IR (KBr)	ν[cm^{-1}] = 3327, 3118, 2922, 1656, 1611, 1452, 1366, 1145, 870, 775, 547		
MS (FAB)	m/z (%) = 484 (MH$^+$, 100)		
NMR CDCl$_3$, 300 MHz	δ[ppm] = 1.46-1.54 (m, 1H, CH-5), 1.88-2.03 (m, 2H, CH$_2$-6), 2.13-2.25, 2.53-2.82 (2×m, 4H, CH$_2$-4, CH$_2$-7), 2.46 (s, 3H, CH$_3$-6'), 3.22-3.38 (m, 2H, CONHC*H*$_2$), 3.78 (s, 3H, CH$_3$-2), 4.29 (s, 2H, PhCH$_2$), 4.53 (s, 2H, NCH$_2$), 6.07 (d, 1H, *J* = 7.54 Hz, CH-5'), 6.95 (broad d, 1H, CONH), 6.98 (s, 1H, CH-3), 7.71-7.30 (m, 5H, Ph), 7.38 (d, 1H, *J* = 7.54 Hz, CH-4'), 8.03 (broad s, 1H, SO$_2$NH).		
CHN for $C_{24}H_{29}N_5O_4S$		Calculated	Found
	% C	59.61	59.05
	% H	6.04	6.02
	% N	14.48	13.71

EXAMPLE 5: Synthesis of (±)-*N*-[(2-amino-5,6,7,8-tetrahydro-6-quinazolinyl)methyl]-2-[3-[(benzyl-sulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide



The title compound was prepared from 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-

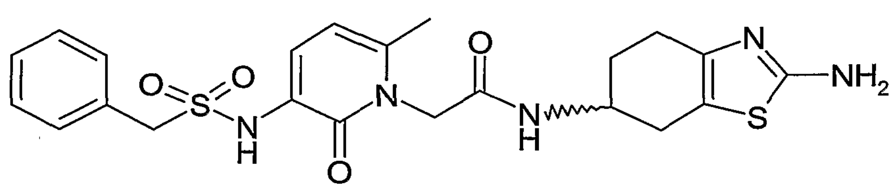
pyridinyl]acetic acid and 6-(aminomethyl)-5,6,7,8-tetrahydro-2-quinazolinamine using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid compound.

η = 44 %

T_{tal} = 210-213°C

(±)-*N*-[(2-amino-5,6,7,8-tetrahydro-6-quinazolinyl)methyl]-2-[3-[(benzyl-sulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3363, 1673, 1644, 1587, 1465, 1355, 1151, 782, 544
MS (FAB)	m/z (%) = 497 (MH^+, 45), 55 (100)
NMR DMSO-d_6, 300 MHz	δ[ppm] = 1.34-1.47 (m, 1H, CH-6), 1.78-1.94 (m, 2H, CH_2-7), 2.27 (s, 3H, CH_3-6'), 2.13-2.26, 2.54-2.67 (2×m, 4H, CH_2-5, CH_2-8), 3.10-3.18 (m, 2H, CONHCH_2), 4.51 (s, 2H, PhCH_2), 4.73 (s, 2H, NCH_2), 6.08 (d, 1H *J* = 7.54 Hz, CH-5'), 6.20 (s, 2H, NH_2-2), 7.13 (d, 1H *J* = 7.54 Hz, CH-4'), 7.20-7.38 (m, 5H, Ph), 7.91 (s, 1H, CH-4), 8.33 (broad t, 1H, CONH), 8.57 (s, 1H, SO_2NH).

EXAMPLE 6: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide



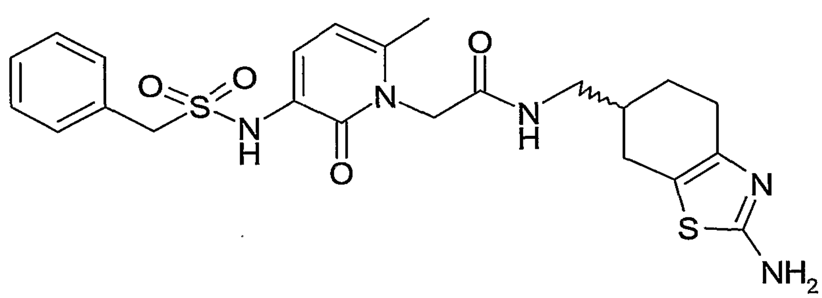
The title compound was prepared from 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-1,3-benzothiazol-2,6-diamine dihydrobromide using the procedure of EXAMPLE 1 (STEP 6), and was obtained as an off-white solid compound.

η = 49 %

T_{tal} = 225-229 °C

(±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3429, 3243, 1705, 1648, 1438, 1302, 1158, 781, 696, 565
MS (FAB)	m/z (%) = 488 (MH^+, 100)
NMR DMSO-d_6, 300 MHz	δ[ppm] = 1.69-1.93, 2.42-2.50, 2.52-2.58, 2.72-2.82 (4×m, 6H, CH_2-4, CH_2-5, CH_2-7), 2.25 (s, 3H, CH_3-6'), 4.03-4.07 (m, 1H, CH-6), 4.51 (s, 2H, $PhCH_2$), 4.71 (s, 2H, NCH_2), 6.08 (d, 1H *J* = 7.53 Hz, CH-5'), 6.66 (s, 2H, NH_2-2), 7.12 (d, 1H, *J* = 7.53 Hz, CH-4'), 7.32-7.37 (m, 5H, Ph), 8.38 (d, 1H, *J* = 7.54 Hz, CONH), 8.54 (s, 1H, SO_2NH).

EXAMPLE 7: Synthesis of (±)-*N*-[(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)methyl]-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide

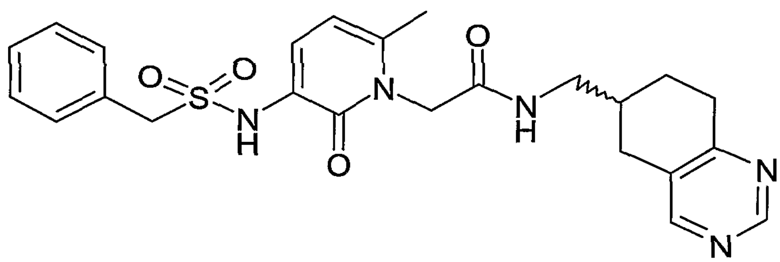


The title compound was prepared from 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 6-(aminomethyl)-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine dihydrobromide using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a pale solid.

η = 41%

(±)-*N*-[(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)methyl]-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3433, 1658, 1600, 1444, 1353, 1152, 789
MS (FAB)	m/z (%) = 502 (MH^+, 36), 154 (100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 1.25-1.35 (m, 1H, CH-6), 1.85-1.93, 2.02-2.13, 2.20-2.30, 2.51-2.77 (4×m, 6H, CH_2-4, CH_2-5, CH_2-7), 2.48 (s, 3H, CH_3-6'), 3.20-3.38 (m, 2H, CONH*CH_2*), 4.33 (s, 2H, $PhCH_2$), 4.63 (s, 2H, NCH_2), 6.04 (d, 1H, *J* = 7.53 Hz, CH-5'), 7.12 (broad s, 1H, NHCO), 7.21-7.33 (m, 7H, Ph, CH-4', $NHSO_2$).

EXAMPLE 8: Synthesis of (±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]-*N*-(5,6,7,8-tetrahydro-6-quinazolinylmethyl)acetamide



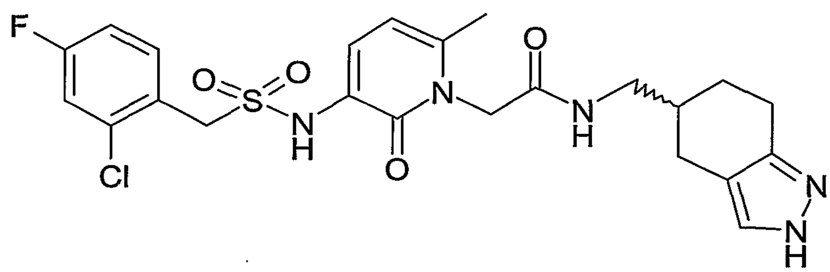
The title compound was prepared from 2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 6-(aminomethyl)-5,6,7,8-tetrahydroquinazoline using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid.

η = 60 %

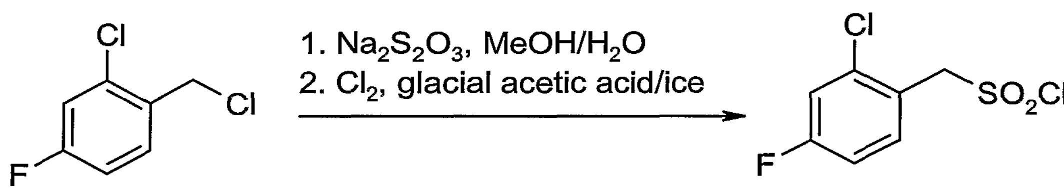
(±)-2-[3-[(benzylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]-*N*-(5,6,7,8-tetrahydro-6-quinazolinylmethyl)acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3374, 1648, 1560, 1457, 1400, 1362, 1152, 894, 778, 698, 544
MS (FAB)	m/z (%) = 482 (MH^+, 37), 154 (100)

NMR DMSO-d_6, 300 MHz	δ[ppm] = 1.53-1.66 (m, 1H, CH-6), 1.94-2.13 (m, 2H, CH_2-7), 2.41-2.13, 2.82-2.98 (2×m, 4H, CH_2-5, CH_2-8), 2.47 (s, 3H, CH_3-6'), 3.17-3.39 (m, 2H, CONH*CH₂*), 4.29 (s, 2H, $PhCH_2$), 4.51 (s, 2H, NCH_2), 6.07 (d, 1H, J = 7.54 Hz, CH-5'), 7.11-7.26 (m, 6H, Ph, NHCO), 7.36 (d, 1H, J = 7.54 Hz, CH-4'), 8.30 (broad s, 1H, $NHSO_2$), 8.36 (s, 1H, CH-4), 8.89 (s, 1H, CH-2).

EXAMPLE 9: Synthesis of (±)-2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide



STEP 1: Synthesis of (2-chloro-4-fluorophenyl)methanesulfonyl chloride

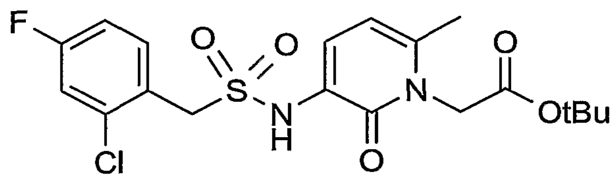


A mixture of 2-chloro-4-fluorobenzyl chloride (7 g, 39.1 mmol) and sodium thiosulfate pentahydrate (9.7 g, 39.1 mmol) in methanol (11 mL) and H_2O (11 mL) was heated to reflux for 3 h. The mixture was cooled to 0°C and glacial acetic acid (11 mL) and ice were added. Chlorine gas was bubbled through the resulting solution for 1 h, periodically adding ice to maintain an ice/liquid mixture. After an additional hour, the reaction was extracted with ether and the ether layer was washed with 5% sodium hydrogen sulphate solution and water, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to give 9.3 g (37.5 mmol) of the title compound as a colourless solid.

η = 98 %

(2-chloro-4-fluorophenyl)methanesulfonyl chloride	
ANALYSIS	RESULTS
NMR $CDCl_3$, 300 MHz	δ[ppm] = 5.09 (s, 2H, CH_2SO_2), 7.13 (ddd, 1H, *J* = 2.63 Hz, *J* = 8.11 Hz, *J* = 8.10 Hz, CH-5), 7.29 (dd, 1H, *J* = 2.63 Hz, *J* = 8.29 Hz, CH-3), 7.62 (dd, 1H, *J* = 5.66 Hz, *J* = 8.67 Hz, CH-6).

STEP 2: Synthesis of *tert*-butyl 2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2H)-pyridinyl]acetate



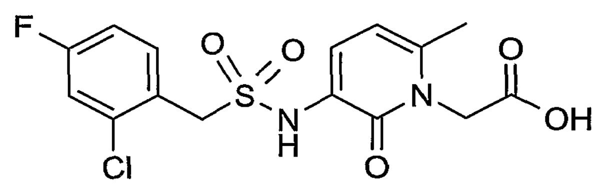
To a solution of *tert*-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (EXAMPLE 1, STEP 1-3), (1.0 g, 4.2 mmol) in dichloromethane (12 mL) and triethylamine (1 mL) cooled to 0°C (2-chloro-4-fluorophenyl)methanesulfonyl chloride (1.2 g, 5.0 mmol) was added in portions. After two hours 10% $KHSO_4$ solution (12 mL) was added. The aqueous phase was extracted with dichloromethane twice. The pooled organic phases were dried over a drying agent and the solvent was evaporated under reduced pressure. The product was purified by column chromatography (silicagel, eluant CH_2Cl_2/MeOH = 30/1) to give 0.77 g (1.73 mmol) of a white solid compound.

η = 41 %

tert-butyl 2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2H)-pyridinyl]acetate	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3128, 2982, 1742, 1652, 1594, 1493, 1447, 1356, 1236, 1157, 918, 856, 771, 596, 493
MS (FAB)	m/z (%) = 445 (MH^+, 50), 55(100)

NMR CDCl$_3$, 300 MHz	δ[ppm] = 1.52 (s, 9H, t-Bu), 2.30 (s, 3H, CH$_3$-6'), 4.53 (s, 2H, PhCH$_2$), 4.77 (s, 2H, NCH$_2$), 6.06 (d, 1H, J = 6.79 Hz, CH-5'), 6.95-7.03 (m, 1H, CH-5), 7.15 (dd, 1H, J = 2.64 Hz, J = 8.67 Hz, CH-3), 7.32 (broad s, 1H, SO$_2$NH), 7.39-7.45 (m, 2H, CH-4', CH-6).

STEP 3: Synthesis of 2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid

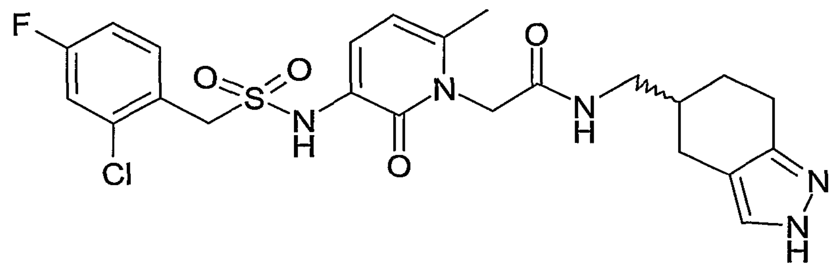


The title compound was prepared from *tert*-butyl 2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl] amino}-6-methyl-2-oxo-1(2H)-pyridinyl]acetate using the procedure of EXAMPLE 1 (STEP 5), and was obtained as a white solid compound.

η = 95 %

2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3247, 2938, 1716, 1657, 1603, 1493, 1440, 1358, 1232, 1148, 1040, 916, 852, 774, 595
MS (FAB)	m/z (%) = 388 (MH$^+$, 24), 181 (100)
NMR DMSO-d$_6$, 300 MHz	δ[ppm] = 2.28 (s, 3H, CH$_3$), 4.65 (s, 2H, PhCH$_2$), 4.80 (s, 2H, NCH$_2$), 6.14 (d, 1H, J = 7.91 Hz, CH-5'), 7.19-7.28 (m, 1H, CH-4', CH-5), 7.47 (dd, 1H, J = 2.63 Hz, J = 9.04 Hz, CH-3), 7.58-7.65 (m, 1H, CH-6) 8.99 (broad s, 1H, SO$_2$NH).

STEP 4: Synthesis of (±)-2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide

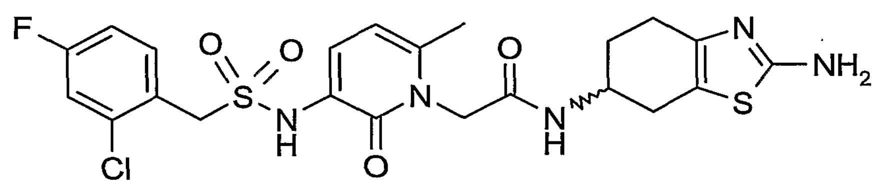


The title compound was prepared from 2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethanamine dihydrochloride using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid compound.

η = 42 %

(±)-2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3302, 2924, 1649, 1599, 1571, 1493, 1443, 1364, 1233, 1156, 1041, 915, 797, 594
MS (FAB)	m/z (%) = 522 (MH^+, 54), 165 (100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 1.42-1.59 (m, 1H, CH-5), 1.87-2.01 (m, 2H, CH_2-6), 2.17-2.26, 2.55-2.70, 2.71-2.81 (3×m, 4H, CH_2-4, CH_2-7), 2.49 (s, 3H, CH_3-6'), 3.21-3.40 (m, 2H, CONHC*H*$_2$), 4.51 (s, 2H, $PhCH_2$), 4.68 (s, 2H, NCH_2), 6.11 (d, 1H, *J* = 7.91 Hz, CH-5'), 6.89-6.97 (m, 2H, CH-5", NHCO), 7.08 (dd, 1H, *J* = 2.63 Hz, *J* = 8.67 Hz, CH-3"), 7.27 (broad s, 1H, SO_2NH), 7.40-7.47 (m, 2H, CH-4', CH-6").

EXAMPLE 10: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl] acetamide

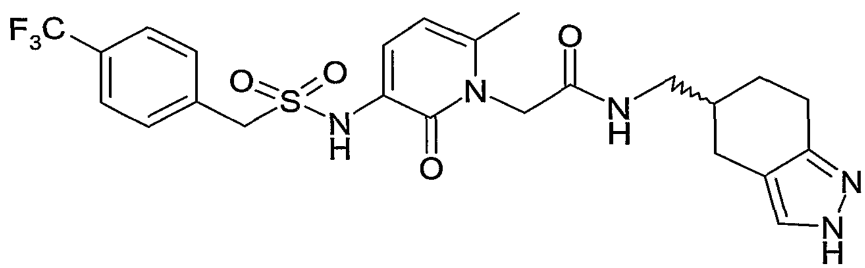


The title compound was prepared from 2-[3-{[(2-chloro-4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-1,3-benzothiazol-2,6-diamine dihydrobromide using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid compound.

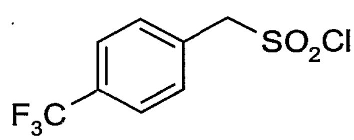
η = 35 %

(±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[3-{[(2-chloro -4-fluorobenzyl)sulfonyl]amino}-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3448, 1655, 1606, 1524, 1491, 1442, 1357, 1231, 1147, 1039, 878, 779, 596
MS (FAB)	m/z (%) = (MH$^+$,), (100)
NMR DMSO-d$_6$, 300 MHz	δ[ppm] = 1.70-1.90, 2.33-2.48, 2.72-2.85 (3×m, 6H, CH_2-4, CH_2-5, CH_2-7), 2.26 (s, 3H, CH_3-6'), 3.98-4.10 (m, 1H, CH-6), 4.65 (s, 2H, PhCH_2), 4.73 (s, 2H, NCH_2), 6.12 (d, 1H *J* = 7.54 Hz, CH-5'), 6.65 (s, 2H, NH_2-2), 7.20 (d, 1H, *J* = 7.54 Hz, CH-4'), 7.20-7.27 (m, 1H, CH-5"), 7.48 (dd, 1H, *J* = 2.64 Hz, *J* = 8.67 Hz, CH-3"), 7.63 (dd, 1H, *J* = 6.41 Hz, *J* = 8.67 Hz, CH-6"), 8.39 (d, 1H, *J* = 7.53 Hz, CONH), 8.91 (s, 1H, SO_2NH).

EXAMPLE 11: Synthesis of (±)-2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl} amino)-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl) acetamide



STEP 1: Synthesis of [4-(trifluoromethyl)phenyl]methanesulfonyl chloride

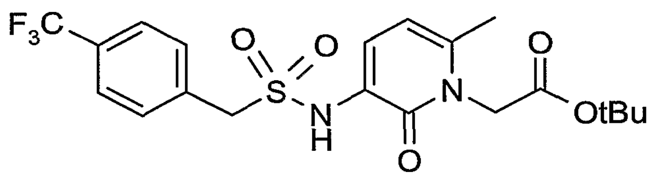


The title compound was prepared from 1-(chloromethyl)-4-(trifluoromethyl)benzene using the procedure of EXAMPLE 9 (STEP 1), and was obtained as a white solid compound.

η = 100 %

[4-(trifluoromethyl)phenyl]methanesulfonyl chloride	
ANALYSIS	RESULTS
IR (KBr)	$\nu[cm^{-1}]$ = 3431, 3004, 1937, 1814, 1619, 1423, 1360, 1325, 1159, 1121, 1069, 1023, 853, 709, 644, 579
NMR CDCl$_3$, 300 MHz	δ[ppm] = 4.92 (s, 2H, CH_2SO_2), 7.65 (d, 2H, *J* = 8.28 Hz, CH-2, CH-6), 7.75 (d, 2H, *J* = 7.91 Hz, CH-3, CH-5).

STEP 2: Synthesis of *tert*-butyl 2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl} amino)-1(2*H*)-pyridinyl]acetate

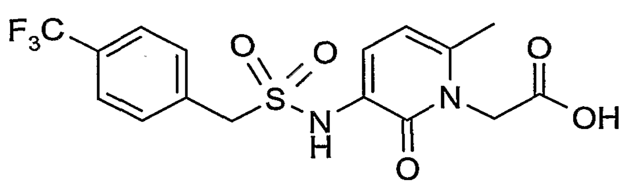


The title compound was prepared from *tert*-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (EXAMPLE 1, STEP 1-3), and [4-(trifluoromethyl)phenyl]methanesulfonyl chloride using the procedure of EXAMPLE 9 (STEP 2), and was obtained as a white solid compound.

η = 32 %

tert-butyl 2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetate	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3232, 2955, 1748, 1718, 1654, 1598, 1530, 1366, 1219, 1149, 1959, 1003, 851, 778, 699
MS (FAB)	m/z (%) = 461 (MH$^+$,17), 91 (100)
NMR CDCl$_3$, 300 MHz	δ[ppm] = 1.49 (s, 9H, t-Bu), 2.27 (s, 3H, CH$_3$-6'), 4.76 (s, 2H, PhCH$_2$), 5.21 (s, 2H, NCH$_2$), 6.11 (d, 1H, *J* = 7.53 Hz, CH-5'), 7.33-7.42 (m, 4H, CH-Ph), 7.77 (broad s, 1H, SO$_2$NH), 7.96 (d, 1H, *J* = 6.78 Hz, CH-4').

STEP 3: Synthesis of 2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetic acid

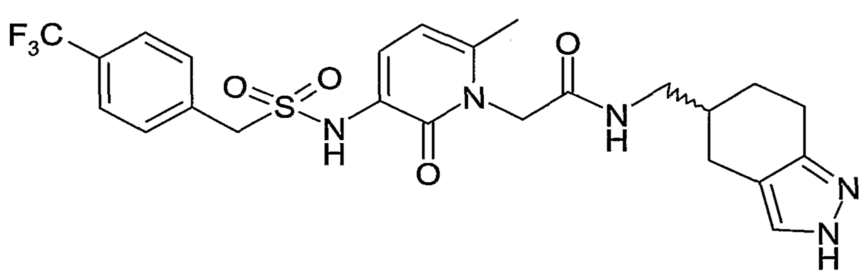


The title compound was prepared from *tert*-butyl 2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetate using the procedure of EXAMPLE 1 (STEP 5), and was obtained as a pail solid compound.

η = 90 %

2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetic acid	
ANALYSIS	RESULTS
IR (KBr)	$\nu[cm^{-1}]$ = 3395, 2960, 1737, 1650, 1557, 1512, 1409, 1182, 1060, 970, 866, 767, 699, 585
MS (FAB)	m/z (%) = 405 (MH^+, 58), 55 (100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 2.35 (s, 3H, CH_3-6'), 4.88 (s, 2H, CH_2Ph), 5.22 (s, 2H, CH_2N), 6.21 (d, 1H, *J* = 7.16 Hz, CH-5'), 7.35-7.42 (m, 4H, CH-Ph), 7.73 (broad s, 1H, $NHSO_2$), 8.03 (d, 1H, *J* = 7.53 Hz, CH-4').

STEP 4: Synthesis of (±)-2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide

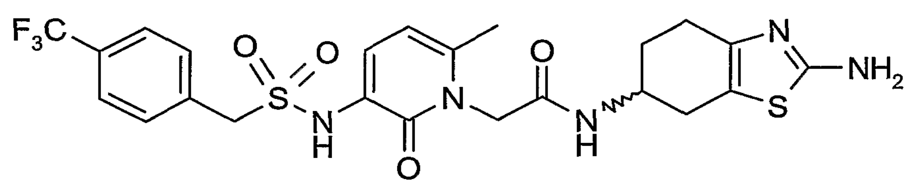


The title compound was prepared from 2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-2*H*-indazol-5-y-lmethanamine dihydrochloride using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid compound.

η = 60 %

(±)-2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide	
ANALYSIS	RESULTS
IR (KBr)	$\nu[cm^{-1}]$ = 3253, 2923, 1713, 1651, 1606, 1536, 1361, 1221, 1092, 717
NMR $CDCl_3$, 300 MHz	δ[ppm] = 1.39-1.52 (m, 1H, CH-5), 1.86-1.97 (m, 2H, CH_2-6), 2.13-2.22, 2.60-2.69, 2.73-2.82 (3×m, 4H, CH_2-4, CH_2-7), 2.27 (s, 3H, CH_3-6'), 3,18-3.36 (m, 2H, CONHCH_2), 4.76 (s, 2H, PhCH_2), 5.23 (s, 2H, NCH_2), 6.19 (d, 1H, *J* = 8.28 Hz, CH-5'), 6.95 (broad t, 1H, NHCO), 7.27 (s, 1H, CH-3), 7.34-7.45 (m, 4H, CH-Ph), 7.74 (broad s, 1H, SO_2NH), 8.01 (d, 1H, *J* = 7.91 Hz, CH-4').

EXAMPLE 12: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl] acetamide



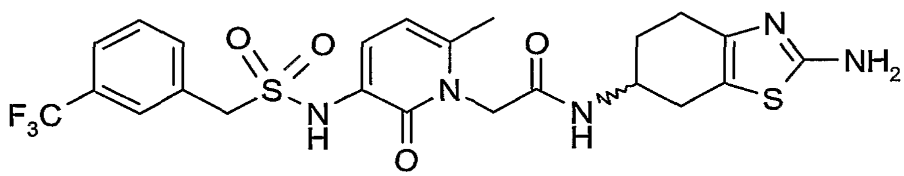
The title compound was prepared from 2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl] sulfonyl}amino)-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-1,3-benzothiazol-2,6-diamine dihydrobromide using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid compound.

η = 37 %

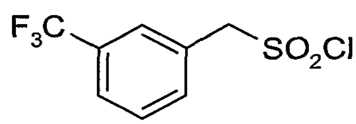
(±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl-2-oxo-3-({[4-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	$\nu[cm^{-1}]$ = 3452, 3386, 3284, 3083, 1732, 1649, 1524, 1416, 1364, 1211, 1090, 849, 697, 618
MS (FAB)	m/z (%) = (MH^+,), (100)

NMR DMSO-d_6, 300 MHz	δ[ppm] = 1.70-1.90, 2.35-2.44, 2.54-2.59, 2.75-2.83 (4×m, 6H, CH_2-4, CH_2-5, CH_2-7), 2.24 (s, 3H, CH_3-6'), 3.96-4.06 (m, 1H, CH-6), 4.71 (s, 2H, $PhCH_2$), 5.16 (s, 2H, NCH_2), 6.16 (d, 1H *J* = 8.29 Hz, CH-5'), 6.64 (s, 2H, NH_2-2), 7.31-7.45 (m, 4H, CH-Ph), 7.72 (d, 1H, *J* = 7.92 Hz, CH-4'), 8.26 (s, 1H, SO_2NH), 8.36 (d, 1H, *J* = 7.16 Hz, CONH).

EXAMPLE 13: Synthesis of *N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl -2-oxo-3-({[3-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetamide



STEP 1: Synthesis of [3-(trifluoromethyl)phenyl]methanesulfonyl chloride

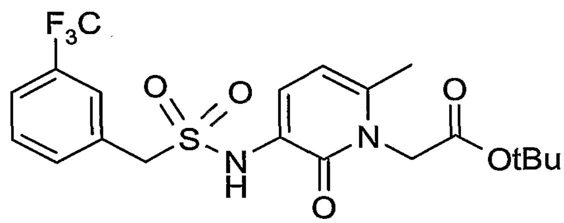


The title compound was prepared from 1-(chloromethyl)-3-(trifluoromethyl)benzene using the procedure of EXAMPLE 9 (STEP 1), and was obtained as a white solid compound.

η = 100 %

[3-(trifluoromethyl)phenyl]methanesulfonyl chloride	
ANALYSIS	RESULTS
NMR $CDCl_3$, 300 MHz	δ[ppm] = 4.94 (s, 2H, CH_2SO_2), 7.60-7.72 (m, 4H, CH-Ph).

STEP 2: Synthesis of *tert*-butyl 2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl)benzyl]sulfonyl} amino)-1(2*H*)-pyridinyl]acetate

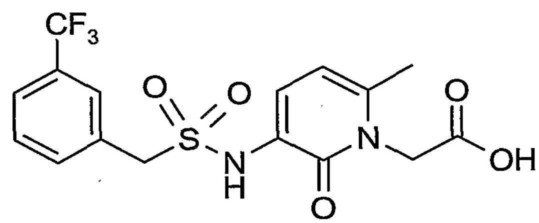


The title compound was prepared from *tert*-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (EXAMPLE 1, STEP 1-3), and [3-(trifluoromethyl)phenyl]methanesulfonyl chloride using the procedure of EXAMPLE 9 (STEP 2), and was obtained as a white solid compound.

η = 33 %

tert-butyl 2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetate	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3152, 2996, 1742, 1651, 1595, 1454, 1334, 1234, 1122, 1073, 1003, 920, 824, 699, 648, 541
MS (FAB)	m/z (%) = 460 (MH$^+$,90), 182 (100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 1.52 (s, 9H, t-Bu), 2.27 (s, 3H, CH_3-6'), 4.40 (s, 2H, $PhCH_2$), 4.76 (s, 2H, NCH_2), 6.02 (d, 1H, *J* = 7.54 Hz, CH-5'), 7.38 (d, 1H, *J* = 7.53 Hz, CH-4'), 7.50-7.70 (m, 5H, CH-Ph, $NHSO_2$).

STEP 3: Synthesis of 2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetic acid

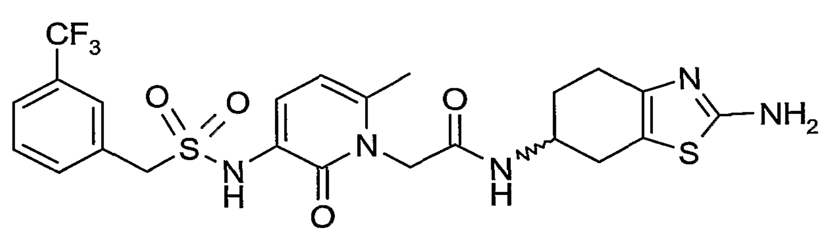


The title compound was prepared from *tert*-butyl 2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl) benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetate using the procedure of EXAMPLE 1 (STEP 5), and was obtained as pail yellow solid compound.

η = 93 %

2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetic acid	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3232, 1722, 1657, 1606, 1452, 1333, 1120, 1074, 1003, 920, 810, 701, 544
MS (FAB)	m/z (%) = 404 (MH^{+}, 39), 159 (100)
NMR CDCl$_3$, 300 MHz	δ[ppm] = 2.32 (s, 3H, CH$_3$-6'), 4.41 (s, 2H, CH$_2$Ph), 4.86 (s, 2H, CH$_2$N), 6.07 (d, 1H, *J* = 8.22 Hz, CH-5'), 7.40 (d, 1H, *J* = 7.91 Hz, CH-4'), 7.52-7.71 (m, 5H, CH-Ph, NHSO$_2$).

STEP 4: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetamide

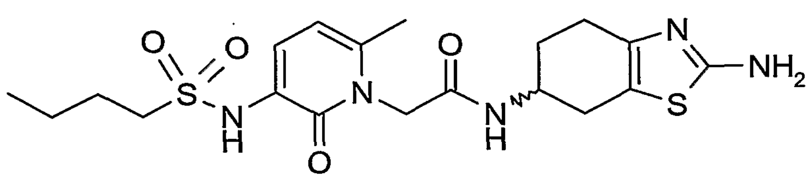


The title compound was prepared from 2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl)benzyl] sulfonyl}amino)-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-1,3-benzothiazol-2,6-diamine dihydrobromide using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a white solid compound.

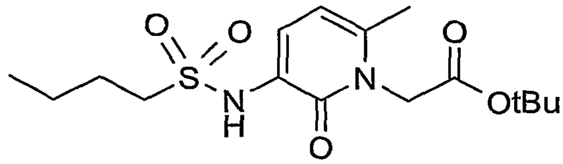
η = 42 %

(±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl-2-oxo-3-({[3-(trifluoromethyl)benzyl]sulfonyl}amino)-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3290, 2934, 1645, 1607, 1531, 1443, 1332, 1148, 1073, 886, 814, 700
MS (FAB)	m/z (%) = (MH^+,), (100)
NMR DMSO-d_6, 300 MHz	δ[ppm] = 1.70-1.90, 2.36-2.43, 2.55-2.59, 2.74-2.84 (4×m, 6H, CH_2-4, CH_2-5, CH_2-7), 2.25 (s, 3H, CH_3-6'), 3.98-4.09 (m, 1H, CH-6), 4.68 (s, 2H, $PhCH_2$), 4.72 (s, 2H, NCH_2), 6.08 (d, 1H *J* = 7.54 Hz, CH-5'), 6.67 (s, 2H, NH_2-2), 7.16 (d, 1H, *J* = 7.16 Hz, CH-4'), 7.58-7.77 (m, 4H, CH-Ph), 8.38 (d, 1H, *J* = 7.91 Hz, CONH), 8.76 (s, 1H, SO_2NH).

EXAMPLE 14: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide



STEP 1: Synthesis of *tert*-butyl 2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate

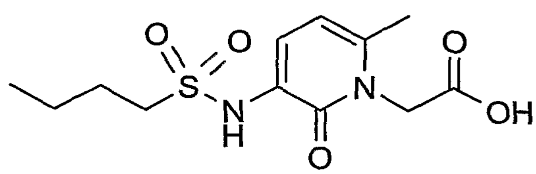


The title compound was prepared from *tert*-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (EXAMPLE 1, STEP 1-3), and 1-butanesulfonyl chloride using the procedure of EXAMPLE 9 (STEP 2). The product was recrystallized from ethylacetate to give a white crystalline solid compound.

η = 49 %

tert-butyl 2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3174, 2973, 1737, 1653, 1600, 1575, 1453, 1357, 1236, 1145, 805, 503
MS (FAB)	m/z (%) = 358 (MH$^+$,100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 0.91 (t, 3H, *J* = 7.16 Hz, CH_3), 1.35-1.46 (m, 2H, CH_2), 1.50 (s, 9H, t-Bu), 1.74-1.85 (m, 2H, CH_2), 2.29 (s, 3H, CH_3-6'), 3.02-3.08 (m, 2H, CH_2), 4.77 (s, 2H, NCH_2), 6.10 (d, 1H, *J* = 7.54 Hz, CH-5'), 7.20 (s, 1H, $NHSO_2$), 7.47 (d, 1H, *J* = 7.53 Hz, CH-4').

STEP 2: Synthesis of 2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid



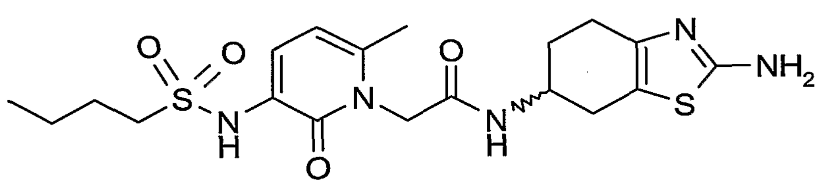
The title compound was prepared from of *tert*-butyl 2-[3-[(butylsulfonyl)amino]-6-methyl-2-

oxo-1(2*H*)-pyridinyl]acetate using the procedure of EXAMPLE 1 (STEP 5), and was obtained as a white crystalline solid compound.

η = 95 %

2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3158, 2938, 1725, 1651, 1604, 1453, 1361, 1248, 1143, 1031, 918, 558
MS (FAB)	m/z (%) = 303 (MH^+, 100)
NMR DMSO-d_6, 300 MHz	δ[ppm] = 0.85 (t, 3H, *J* = 7.16 Hz, CH_3), 1.26-1.43 (m, 2H, CH_2), 1.61-1.72 (m, 2H, CH_2), 2.27 (s, 3H, CH_3-6'), 3.03-3.11 (m, 2H, CH_2), 4.77 (s, 2H, NCH_2), 6.17 (d, 1H, *J* = 7.54 Hz, CH-5'), 7.29 (d, 1H, *J* = 7.53 Hz, CH-4') 8.68 (s, 1H, $NHSO_2$).

STEP 3: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide

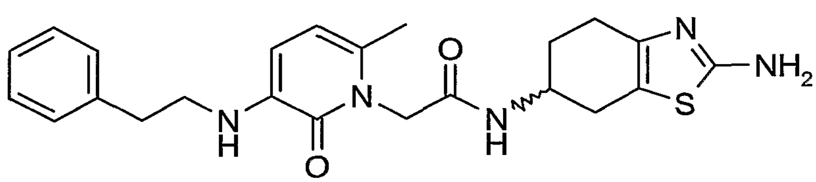


The title compound was prepared from 2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-1,3-benzothiazol-2,6-diamine dihydrobromide using the procedure of EXAMPLE 1 (STEP 6) The product was recrystallized from methanol to give a pale brown solid compound.

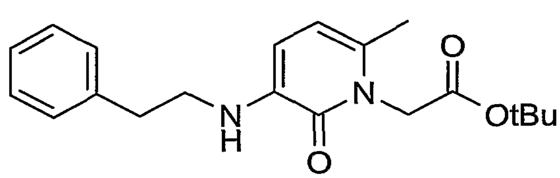
η = 40 %

(±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[3-[(butylsulfonyl)amino]-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3464, 3324, 3136, 2953, 1649, 1594, 1449, 1354, 1143, 775, 559
MS (FAB)	m/z (%) = 454 (MH^+, 49), 154 (100)
NMR DMSO-d_6, 300 MHz	δ[ppm] = 0.85 (t, 3H, *J* = 7.53 Hz, CH_3), 1.28-1.40 (m, 2H, CH_2), 1.61-1.72 (m, 2H, CH_2), 1.73-1.90, 2.33-2.44, 2.53-2.59, 2.72-2.82 (4×m, 6H, CH_2-4, CH_2-5, CH_2-7), 2.26 (s, 3H, CH_3-6'), 3.03-3.10 (m, 2H, CH_2), 3.95-4.05 (m, 1H, CH-6), 4.70 (s, 2H, NCH_2), 6.13 (d, 1H *J* = 7.53 Hz, CH-5'), 6.65 (s, 2H, NH_2-2), 7.27 (d, 1H, *J* = 7.54 Hz, CH-4'), 8.36 (d, 1H, *J* = 7.92 Hz, CONH), 8.59 (s, 1H, SO_2NH).

EXAMPLE 15: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetamide



STEP 1: Synthesis of *tert*-butyl 2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl] acetate



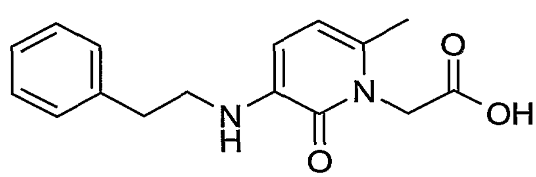
Sodium triacetoxyborohydride (0.67 g, 3.15 mmol) was added to a stirred solution of *tert*-butyl 2-[3-amino-6-methyl-2-oxo-1(2*H*)-pyridinyl]acetate (EXAMPLE 1, STEP 1-3), (0.5 g, 2.10 mmol) and phenyl acetaldehyde (0.18 mL, 2.33 mmol) in 0.24 M acetic acid (0.14 mL) in 1,2-dichloroethane (11 mL). After 16 h the mixture was quenched with water and extracted

into ethylacetate. The ethyl acetate layer was washed with sodium carbonate solution and brine, dried (Na_2SO_4) and evaporated under reduced pressure to a glass. The crude product was purified by flash column chromatography (silicagel, eluant CH_2Cl_2/MeOH = 40/1) to give 0.34 g (1.00 mmol) of a light blue solid compound.

η = 47 %

tert-butyl 2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetate	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3337, 2976, 1748, 1649, 1596, 1493, 1364, 1156, 943, 700
MS (FAB)	m/z (%) = 343 (MH^+,65), 93 (100)
NMR $CDCl_3$, 300 MHz	δ[ppm] = 1.50 (s, 9H, t-Bu), 2.21 (s, 3H, CH_3-6'), 2.88-2.97 (m, 2H, CH_2), 3.33 (t, 2H, *J* = 7.35 Hz, CH_2), 4.77 (s, 2H, NCH_2), 4.87 (broad s, 1H, NH), 6.00 (d, 1H, *J* = 7.16 Hz, CH-5'), 6.18 (d, 1H, *J* = 7.16 Hz, CH-4'), 7.23-7.37 (m, 5H, Ph).

STEP 2: Synthesis of 2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetic acid



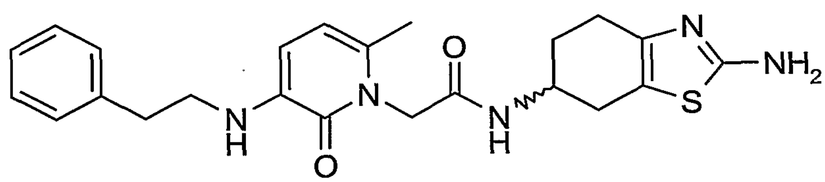
The title compound was prepared from of *tert*-butyl 2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetate using the procedure of EXAMPLE 1 (STEP 5), and was obtained as a yellow solid compound.

η = 96 %

2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetic acid	
ANALYSIS	RESULTS
MS (FAB)	m/z (%) = 287 (MH^+, 100)

NMR DMSO-d_6, 300 MHz	δ[ppm] = 2.17 (s, 3H, CH-6'), 2.86 (t, 2H, *J* = 7.35 Hz, CH_2) 3.25 (t, 2H, *J* = 7.35 Hz, CH_2), 4.72 (s, 2H, NCH_2), 6.02 (d, 1H, *J* = 8.29 Hz, CH-5'), 6.29 (d, 1H, *J* = 7.53 Hz, CH-4'), 7.19-7.33 (m, 5H, Ph).

STEP 3: Synthesis of (±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetamide

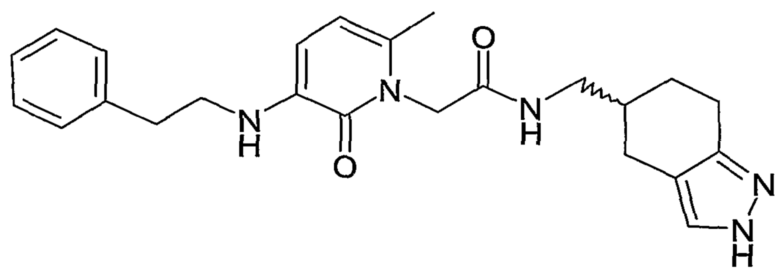


The title compound was prepared from 2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-1,3-benzothiazol-2,6-diamine dihydrobromide using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a yellow crystalline solid compound.

η = 40 %

(±)-*N*-(2-amino-4,5,6,7-tetrahydro-1,3-benzothiazol-6-yl)-2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3418, 1644, 1593, 1524, 1369, 1333, 1232, 779, 700
MS (FAB)	m/z (%) = 437 (MH^+, 65), 269 (100)
NMR DMSO-d_6, 300 MHz	δ[ppm] = 1.67-1.90, 2.33-2.45, 2.51-2.82 (3×m, 6H, CH_2-4, CH_2-5, CH_2-7), 2.15 (s, 3H, CH_3-6'), 3.94-4.08 (m, 1H, CH-6), 4.65 (s, 2H, NCH_2), 5.02 (broad t, 1H, NH), 5.98 (d, 1H, *J* = 7.53 Hz, CH-5'), 6.22 (d, 1H, *J* = 7.53 Hz, CH-4'), 6.65 (s, 2H, NH_2-2), 7.18-7.34 (m, 5H, Ph), 8.27 (d, 1H, *J* = 7.54 Hz, CONH).

EXAMPLE 16: Synthesis of (±)-2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide

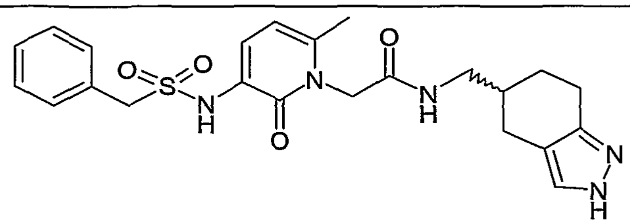
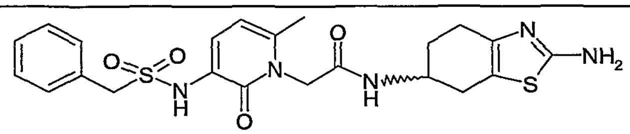
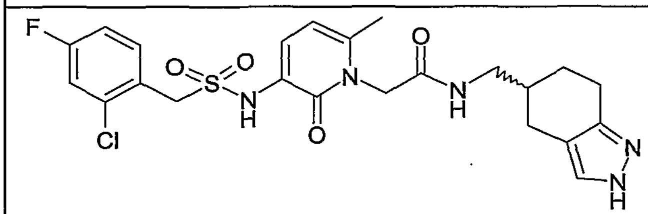
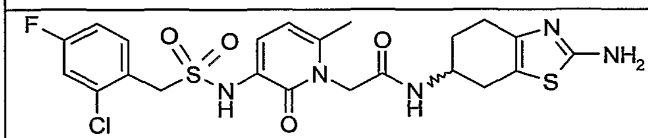
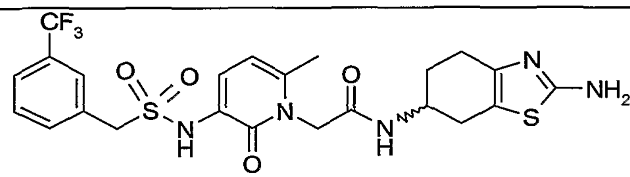
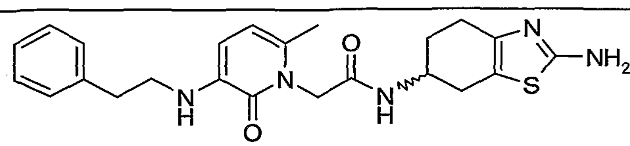
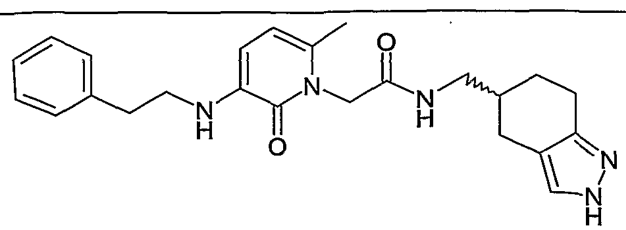


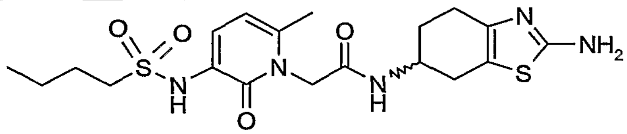
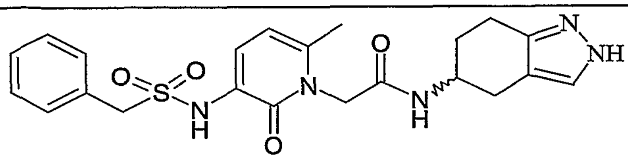
The title compound was prepared from 2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]acetic acid and 4,5,6,7-tetrahydro-2*H*-indazol-5-ylamine dihydrochloride using the procedure of EXAMPLE 1 (STEP 6), and was obtained as a yellow solid compound.

η = 45 %

(±)-2-[6-methyl-2-oxo-3-(phenethylamino)-1(2*H*)-pyridinyl]-*N*-(4,5,6,7-tetrahydro-2*H*-indazol-5-ylmethyl)acetamide	
ANALYSIS	RESULTS
IR (KBr)	ν[cm^{-1}] = 3291, 2924, 1645, 1593, 1492, 1361, 1236, 1112, 960, 752, 701
MS (FAB)	m/z (%) = (MH$^+$,), (100)
NMR CDCl$_3$, 300 MHz	δ[ppm] = 1.38-153 (m, 1H, CH-5), 1.81-1.97 (m, 2H, CH$_2$-6), 2.07-2.20, 2.51-2.81 (2×m, 4H, CH$_2$-4, CH$_2$-7), 2.39 (s, 3H, CH$_3$-6'), 2.95 (t, 2H, *J* = 7.35 Hz, CH$_2$), 3.19-3.29 (m, 2H, NHCO*CH$_2$*) 3.34 (t, 2H, *J* = 7.16 Hz, CH$_2$), 4.75 (s, 2H, NCH$_2$), 6.07 (d, 1H, *J* = 7.54 Hz, CH-5'), 6.23 (d, 1H, *J* = 7.53 Hz, CH-4'), 7.14 (broad t, 1H, NHCO), 7.20-7.35 (m, 6H, Ph, CH-3).

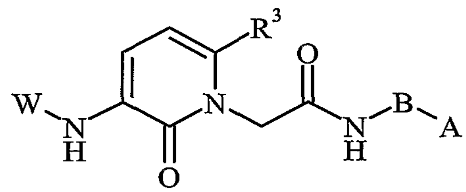
EXAMPLE 17: Results of tested compounds regarding the inhibition of thrombin and trypsin

Compound structure	Ki thrombin (μM)	Ki trypsin (μM)	Ki trypsin/ Ki thrombin
	0.21	376	1790
	0.16	260	1625
	0.16	>300	>1875
	0.16	193	1097
	0.65	>200	>300
	0.69	147	213
	0.82	421	526

	1.3	50	37
	4.7	438	93

CLAIMS

1. Compounds of the general formula (I)



(I)

wherein:

W is

R^1,

R^1OCO,

R^1CO,

R^1SO_2,

$(R^1(CH_2)_n)_mNH_qCO$, where n is 0, 1, 2, 3 or 4,
where m is 1 or 2 and
where q is 0 or 1, with the proviso
that where n is 1, 2, 3 or 4, q is 1 and m is 1, and
where n is 0, m is 1 or 2 and q is 0 or 1,
and wherein R^1 can be the same or different;

R^1 is

$R^2(CH_2)_n$, where n is 0, 1, 2, 3 or 4,

$(R^2)(OR^2)CH(CH_2)_p$, where p is 1, 2, 3 or 4,

$(R^2)_2CH(CH_2)_n$, where n is 0, 1, 2, 3 or 4, and R^2 can be the same or different, and

$R^2O(CH_2)_p$, where p is 1, 2, 3 or 4;

R^2 is

hydrogen,

phenyl, unsubstituted or substituted with one or more C_{1-4} linear or branched alkyl, C_{1-4} linear or branched alkoxy, halogen,

trifluoromethyl, hydroxy, $COOR^4$, $CONHR^4$, nitro, NHR^4 or NR^4R^4 group(s),

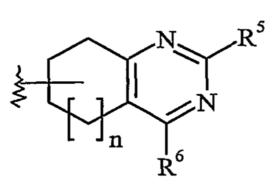
naphthyl,
biphenyl,
5- to 7-membered monocyclic or 9- to 10- membered bicyclic heterocyclic ring system which can be substituted or unsubstituted and, which in addition to carbon atoms, contains up to 3 heteroatoms selected from N, O and S,
$COOR^4$,
C_{1-4} linear or branched alkyl,
C_{3-7} cycloalkyl, or
C_{7-12} bicycloalkyl;

R^4 is
hydrogen, or
C_{1-4} linear or branched alkyl;

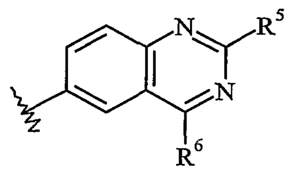
R^3 is
hydrogen,
C_{1-4} linear or branched alkyl,
C_{3-7} cycloalkyl, or
trifluoromethyl group;

B is
$(CH_2)_k$, where k is 0 or 1;

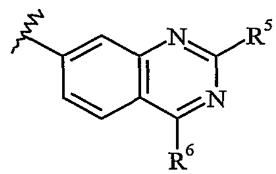
A is chosen from one of the following radicals:



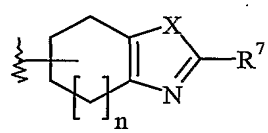
wherein n = 0, 1 ,



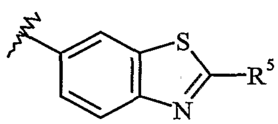
,



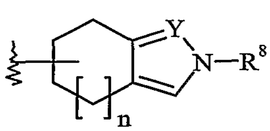
,



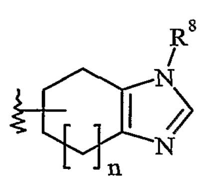
wherein X is S, NH or O and n = 0 or 1,



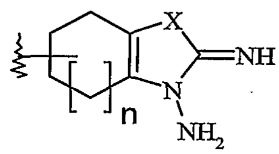
,



wherein Y is N or CH and n = 0 or 1 ,



wherein n = 0 or 1 ,



wherein X is O or S and n = 0 or 1;

R^5 is

hydrogen or NH_2;

R^6 is

hydrogen or NH_2;

R^7 is

hydrogen, NH_2 or $NHC(NH)NH_2$;

R^8 is

hydrogen, CH_3, ethyl, propyl, cyclopropyl or $C(NH)NH_2$.

2. The Compounds of claim 1, being in the form of racemates, racemic mixtures, pure enantiomers, mixtures of diastereomers or pure diastereomers.

3. The compounds of claim 1 or 2, being a pharmaceutically acceptable salt thereof

4. Compounds of formula (I) according to any one of claims 1 to 3 for use in therapy.

5. Use of compounds of formula (I) according to any one of claims 1 to 3 in the manufacture of medicaments for inhibiting thrombin and fibrin formation and for inhibiting thrombus formation.

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 3 and pharmaceutically acceptable auxiliary substances.

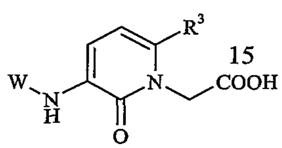
7. Use of pharmaceutical compositions of Claim 6 for inhibiting thrombin in blood of man and other mammals.

8. Use of pharmaceutical compositions of Claim 6 for inhibiting formation of fibrin in blood of man and other mammals.

9. A method for inhibiting thrombin in blood of man and other mammals comprising administering a compound of the formula (I) according to any one of claims 1 to 3.

10. A method for inhibiting fibrin and thrombus formation in man and other mammals comprising administering a therapeutically effective amount of a compound of the formula (I) according to any one of claims 1 to 3.

11. A process for the preparation of compounds of the formula (I) according to any one of claims 1 to 3 characterised in that the fragment



is condensed with the fragment A-B-NH_2 by using reagents for the peptide bond formation, wherein R^3, W, A and B have the same meaning as in Claim 1.

12. The process of claim 11, wherein the fragment A is protected by a protecting group, and the process further comprises the step of removing the protecting group after the condensation reaction.

INTERNATIONAL SEARCH REPORT

PCT/IB 02/05079

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D417/04 A61K31/4436 A61K31/4439 A61K31/444
A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 79195 A (HO JONATHAN ZHANGI; CUI JINGJONG JEAN (US); LEVY ODILE ESTHER (US)) 25 October 2001 (2001-10-25) claims 1,2,41-44,102,103; figures 1-6; examples 12,25,26,30,36,43,62,70-75,83,84,86,101 ---	1-12
Y	WO 01 79262 A (CORVAS INT INC; ARALDI GIAN LUCA (US); SEMPLE JOSEPH EDWARD (US)) 25 October 2001 (2001-10-25) claims 1,36,45; figures 1-6; examples 12,25,26,30,36,43,62,70-75,83,84,86,101 ---	1-12
Y	WO 99 61442 A (NAYLOR OLSEN ADEL M; MERCK & CO INC (US); SANDERSON PHILIP E (US)) 2 December 1999 (1999-12-02) claims; examples 8,9; table 1 ---	1-10
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2003	03/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hass, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 46207 A (ARDECKY ROBERT JOHN; RIPKA WILLIAM CHARLES (US); GE YU (US); CORVA) 11 December 1997 (1997-12-11) claims; figures; examples	1-12
A	WO 97 01338 A (NAYLOR OLSEN ADEL M; DYER DONA L (US); FRALEY MARK E (US); DORSEY) 16 January 1997 (1997-01-16) page 16 -page 25; claims	1-12
A	US 5 668 289 A (NAYLOR-OLSEN ADEL M ET AL) 16 September 1997 (1997-09-16) column 9 -column 18; claims	1-12
A	WO 97 30708 A (BRADY STEPHEN F; LUMMA WILLIAM C (US); LYLE TERRY A (US); MERCK &) 28 August 1997 (1997-08-28) scheme 1; claims	1-12
A	WO 01 04117 A (DIMENSIONAL PHARM INC) 18 January 2001 (2001-01-18) example 2	1-10
A	WO 98 42342 A (NAYLOR OLSEN ADEL M; DORSEY BRUCE D (US); MERCK & CO INC (US); ISA) 1 October 1998 (1998-10-01) claims	1-10

INTERNATIONAL SEARCH REPORT

PCT/IB 02/05079

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/IB 02/05079

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0179195	A	25-10-2001	AU	5539901	A	30-10-2001
			WO	0179195	A2	25-10-2001
WO 0179262	A	25-10-2001	US	6506754	B1	14-01-2003
			AU	5540901	A	30-10-2001
			WO	0179262	A1	25-10-2001
WO 9961442	A	02-12-1999	AU	742178	B2	20-12-2001
			AU	4096999	A	13-12-1999
			CA	2333040	A1	02-12-1999
			EP	1082324	A1	14-03-2001
			JP	2002516326	T	04-06-2002
			WO	9961442	A1	02-12-1999
			US	6093717	A	25-07-2000
WO 9746207	A	11-12-1997	US	6011158	A	04-01-2000
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